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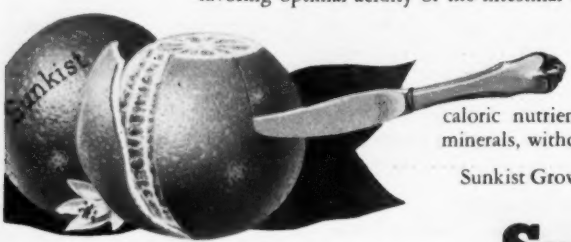

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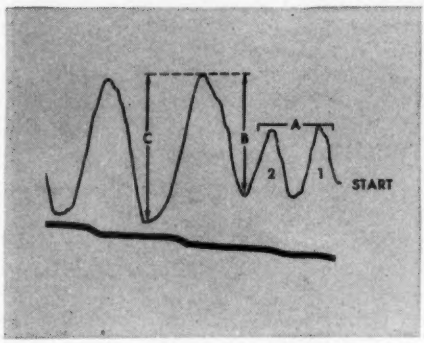

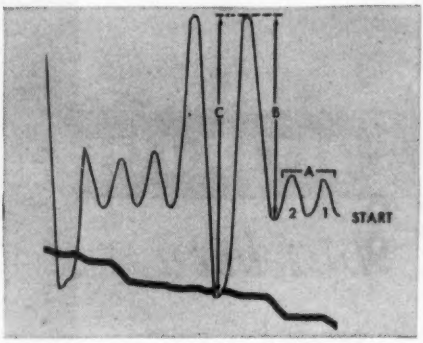

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Schwartz, E., *J.A.M.A.* **147**: 1734–1737. Dec. 29, 1951.

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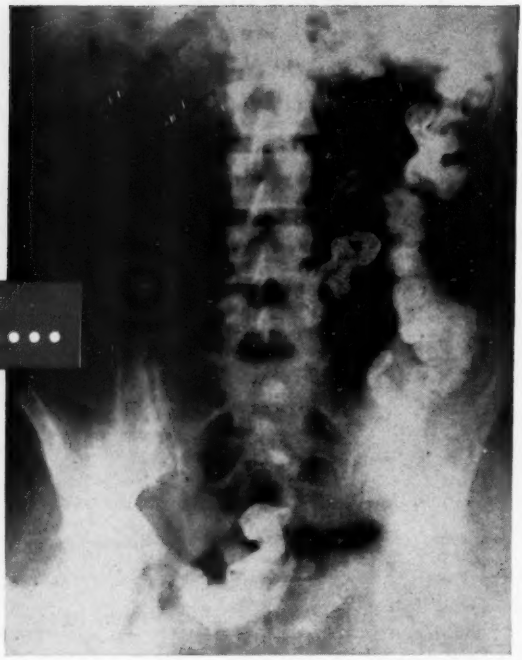

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*Barowsky, H.: A Roentgenographic Evaluation of the Common Measures Employed in the Treatment of Colonic Stasis, Rev. Gastroenterol. *19*:154 (Feb.) 1952.

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**

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Editorials

UNTOWARD EFFECTS ON THE STOMACH OF CORTICOTROPIN AND CORTISONE

ALTHOUGH much has been written about the untoward reactions which may follow the administration of corticotropin (ACTH) and cortisone, gastrointestinal complications seem to be rare. In Thayer's recent analysis,[1] for example, of 66 patients who had been treated with these agents, only one complained of postprandial epigastric distress, which disappeared when corticotropin therapy was stopped. Nonetheless, a severe gastrointestinal disturbance may occasionally be caused by corticotropin or cortisone:

A middle-aged man had severe rheumatoid arthritis which prevented him from carrying on his work. Cortisone was given in full doses in the hope of relieving his pain. He had never had any stomach trouble before but, while receiving cortisone, soon had epigastric distress followed by a large hematemesis. There was high gastric acidity (histamine), and the roentgenogram showed a typical ulcer on the lesser curvature with a crater nearly 1 cm. deep. Cortisone administration was promptly discontinued, the epigastric distress subsided, and the roentgen appearance became normal. In spite of all this, it was thought wise to explore the stomach, but on operation (gastrotomy) an inspection of the mucosa showed no trace of ulcer or even a scar. Meanwhile, the arthritis had become much worse again, so that cortisone therapy was resumed. Within a few days epigastric distress returned and roentgenograms once more showed a definite ulcer crater on the lesser curvature. In this unusual case, therefore, the taking of cortisone was very promptly followed by increased gastric acidity, indigestion, and actual gastric ulcer.

Gray and his associates [2] have recently studied gastric secretion, by careful quantitative methods, before and after the administration of corticotropin. It turns out that the concentration of acid in the stomach juice may increase within one to two or three weeks by as much as 200 or 300%. There is a corresponding increase in pepsin, but the volume of secretion is little altered. By no means all of Gray's subjects, however, exhibited symptoms or evidence of actual ulcer; this fits in with general experience in the field.

It has long been held by many students of the ulcer problem that, while acid and pepsin play an important and indeed perhaps essential role in the production of peptic ulcer, a constitutional predisposition is also necessary; without this "diathesis," even though acid is high, as it may be in many healthy persons, no gastroduodenal ulceration seems to occur. Although it is to be expected that preexisting

1. Thayer, J. M.: Side Effects of Cortisone and ACTH, Stanford M. Bull. **10**:1, 1952.

2. Gray, S. J.; Benson, J. A., Jr.; Reifenstein, R. W., and Spiro, H. M.: Chronic Stress and Peptic Ulcer: I. Effect of Corticotropin (ACTH) and Cortisone on Gastric Secretion, J. A. M. A. **147**:1529, 1951.

ulcer will be reactivated by cortisone or corticotropin, it is also probable that the person with ulcer "diathesis" who has not previously had clinical trouble will be precipitated into difficulties if he receives these agents, as in the case reported above.

This line of thought leads to the suggestion that much valuable information about the pathogenesis of peptic ulcer could be obtained by making careful measurements of gastric secretion, and roentgenograms, on large numbers of persons before and after administration of corticotropin or cortisone; the findings could then be correlated with previous evidence of peptic ulcer, hyperacidity, or indigestion in relation to any untoward effects which might follow the use of these agents. Equally interesting would be a study of the effects on cortisone-induced hyperacidity of drugs which are used to inhibit gastric secretion, such as atropine and methantheline (banthine®)—or indeed vagotomy. If, as has been suggested,[2] postcortisone hyperacidity is a direct hormonal effect on gastric cells and is not mediated through the autonomic nerves, it may be necessary to control such excessive secretion by alkalis (other than sodium) and perhaps by anion-exchange resins rather than by agents which inhibit the vagus. At any rate, with cortisone and corticotropin we may now have a tool which will be of great value in solving some of the long-disputed problems about the nature of peptic ulcer.

Needless to say, the validity of studies of gastric secretion depends on the use of accurate methods. Whether one collects the "basal" secretions or the gastric juice produced by histamine stimulation, considerable skill and experience are necessary on the part of the operator if quantitative results useful for comparative purposes on successive examinations are to be obtained. It is absolutely necessary to keep up continuous aspiration by means of a syringe constantly manipulated by hand if anything approaching a complete collection of juice is to be obtained. It also requires long training and experience before the operator develops a tactile sense which enables him to tell when the stomach is relaxed or in spasm. Despite the emphasis which has often been placed on these points, it is common practice to have miscellaneous technicians, students, or nurses carry out gastric aspiration. The results obtained in this way often have no quantitative value and, indeed, may be downright misleading. The same can be said of the common practice of attaching suction to a tube placed in the stomach in the hope of collecting all the secretions. An error is introduced because under these conditions an unknown amount of juice runs out through the pylorus and is lost; continuous manual suction by means of a syringe by an operator skilled in appreciating the alternate phases of tonus and relaxation of the stomach is absolutely necessary for really accurate results.

The histamine test for comparative measurements of gastric secretion has been criticized by some as giving variable results in the same person on successive occasions,[3] even under similar conditions. This has not been true in our experience if the test is done by those experienced in the procedure. In 46 consecutive multiple (two to four) histamine tests, the pattern was always the same, and at most there was a difference in clinical units of 10 or 15%. In no case did a person with

3. Watkinson, G., and James, A. H.: Twenty-Four Hour Gastric Analysis in Patients with Histamine Achlorhydria, Clin. Sc. **10**:255, 1951 (references to literature)

histamine anacidity later show a high degree of acid or vice versa. One must be just as careful with this test as with bone marrow puncture, study of urinary sediment, or any other quantitative examination.

In connection with this whole subject, one should mention the method described by Segal, Miller, and Morton [4] for determination of gastric acidity without intubation. An exchange resin called quininium resin indicator is given by mouth. If free hydrochloric acid is present, the quininium cation appears in the urine. By noting the appearance time and by means of photofluorometric readings, quantitative estimations of gastric acidity can be made. This method seems worthy of thorough trial, and for the purpose of repeated comparative measurements will be particularly useful if its reliability is confirmed.

ARTHUR L. BLOOMFIELD, M.D.

4. Segal, H. L.; Miller, L. L., and Morton, J. J.: Determination of Gastric Acidity Without Intubation by Use of Cation Exchange Indicator Compounds, Proc. Soc. Exper. Biol. & Med. **74**:218, 1950.

PERIPHERAL VASCULAR MURMURS

Mechanism of Production and Diagnostic Significance

EDWARD A. EDWARDS, M.D.
AND
HAROLD D. LEVINE, M.D.
BOSTON

WHILE it is commonplace in clinical procedure to hear murmurs over peripheral aneurysms and arteriovenous fistulae, it is but little appreciated that murmurs may also be heard over blood vessels in a great variety of conditions, particularly those characterized by a reduction in size of the vascular lumen. This paper is concerned with such locally generated murmurs in both arteries and veins, the mechanism of their formation, and their diagnostic significance. Optically registered examples of such murmurs will be presented, correlated in some instances with the roentgenangiograms. This clinical material will be preceded by an analysis of the theory of murmur formation. A presentation of experimental murmur formation by pneumatic cuff compression in normal subjects will also be offered in explanation of the murmurs encountered in obstructive lesions of the blood vessels.

There are three distinct aspects to the problem of formation and appreciation of murmurs: the mechanism of their formation, with which this report is mainly concerned; the transmission through the tissues of the vibrations involved, about which little is known, and their detection either by the ear or by instrumental means. It may be worth noting that the apparatus presently available for recording is defective in that some frequencies are absorbed and fail to be recorded.

The apparatus used for the registration of the murmurs in this study, except in the experiment noted, consisted of the Maico Stethetron device (an electronic stethoscope) connected to the Sanborn multiple-channel amplifier-tube electrocardiograph. The microphone placed over the vessel is of piezoelectric design. A "tone selector" and volume control are interposed between the microphone and the electrocardiograph. A simultaneous recording of the Lead II electrocardiogram or of the pulse wave over the contralateral artery allowed a determination of the pulse phase of the sound vibrations. All the tracings shown, with exceptions as later noted, were made at a paper speed of 25 mm. per second.

Read before the meeting of the New England Surgical Society, March 28, 1951.

This study was aided by a grant from the Plymouth Chapter of the Massachusetts Heart Association.

From the Department of Surgery and the Medical Clinic of the Peter Bent Brigham Hospital, and the Departments of Anatomy and Medicine of the Harvard Medical School.

Dr. Edwards is Associate in Surgery, Peter Bent Brigham Hospital, and Assistant Clinical Professor of Anatomy, Harvard Medical School. Dr. Levine is Associate in Medicine, Peter Bent Brigham Hospital, and Clinical Associate in Medicine, Harvard Medical School.

THEORETICAL CONSIDERATIONS

Excluding the brief sound in earliest systole, normal blood flow does not give rise to murmur formation. Vibrations arising under abnormal conditions and appreciated as murmurs may theoretically be engendered either in the blood stream or in the vessel wall. The mechanisms which may operate in either location are summarized in Figure 1 and are explained in detail below. The classification is based partly on the observations of Sahli [1] and of Bondi.[2]

Vibrations Arising in the Blood Stream.—Undoubtedly most of the vascular murmurs encountered clinically have their origin in vibrations of the blood itself [3]; Turbulent flow is generally spoken of as existing when sound is present, but turbulence is not necessarily productive of sound, and it is, therefore, more accurate to use the term "vibration-producing" in this connection. A change from the usual stream line to turbulent flow occurs when the so-called Reynolds number is attained according to the following expression [4]:

$$\text{Reynolds Number} = \frac{\text{Radius of Vessel} \times \text{Velocity} \times \text{Density of the Fluid}}{\text{Viscosity of the Fluid}}$$

Notwithstanding the fact that it is uncertain that this formula is precisely applicable to vibration production in a numerical way, the factors are significant in the causation of murmurs. Only changes in the radius of the vessel and the velocity of the blood stream are of practical importance in the present problem. Increase in size of the vessel is perhaps most important in murmur formation in an arterial aneurysm. In other vessel disorders the production of a high velocity appears to be the significant factor. Velocity may be altered by changes in the blood pressure or in the caliber of the vessel, since velocity is directly proportionate to pressure and inversely proportionate to vessel size.

The effect of pressure in increasing velocity and thus inducing vibration is indicated in many vascular murmurs.[5] Thus, an arterial murmur is usually present only during systole, when the pressure, and correspondingly the velocity of the blood stream, is at its height. Often a murmur becomes audible only when the pulse pressure is increased by exercise or by the administration of epinephrine.

Narrowing of the vessel, with corresponding increase in velocity, is also a frequent source of sound production. It is the basis for the greater part of the Korotkoff sound in sphygmomanometry and for the systolic murmur over segments of arteriosclerotic narrowing. Gupta and Wiggers,[6] studying experimental aortic coarctation, have noted that the magnitude of the constriction is not strictly proportionate to the intensity of the murmur. A murmur occurred when 60% of the aortic lumen was occluded, reached its greatest intensity at 73%, and was no longer

1. Sahli, H.: A Treatise on Diagnostic Methods of Examination, Ed. 2, translated by N. D. Potter, Philadelphia, W. B. Saunders Company, 1911.

2. Bondi, S.: Die Entstehung der Herzgeräusche, Ergebn. inn. Med. u. Kinderh. **50**:308, 1936.

3. Sahli.[1] Bondi.[2]

4. Ponder, E.: Velocity and Pressure of Blood Flow, in Howell, W. H.: Textbook of Physiology, Ed. 15, edited by J. E. Fulton, Philadelphia, W. B. Saunders Company, 1946.

5. Lewis, J. K., and Hewlett, A. W.: The Cause of Increased Vascular Sounds After Epinephrin Injection, Heart **10**:1, 1923.

6. Gupta, T. C., and Wiggers, C. J.: Basic Hemodynamic Changes Produced by Aortic Coarctation of Different Degrees, Circulation **3**:17, 1951.

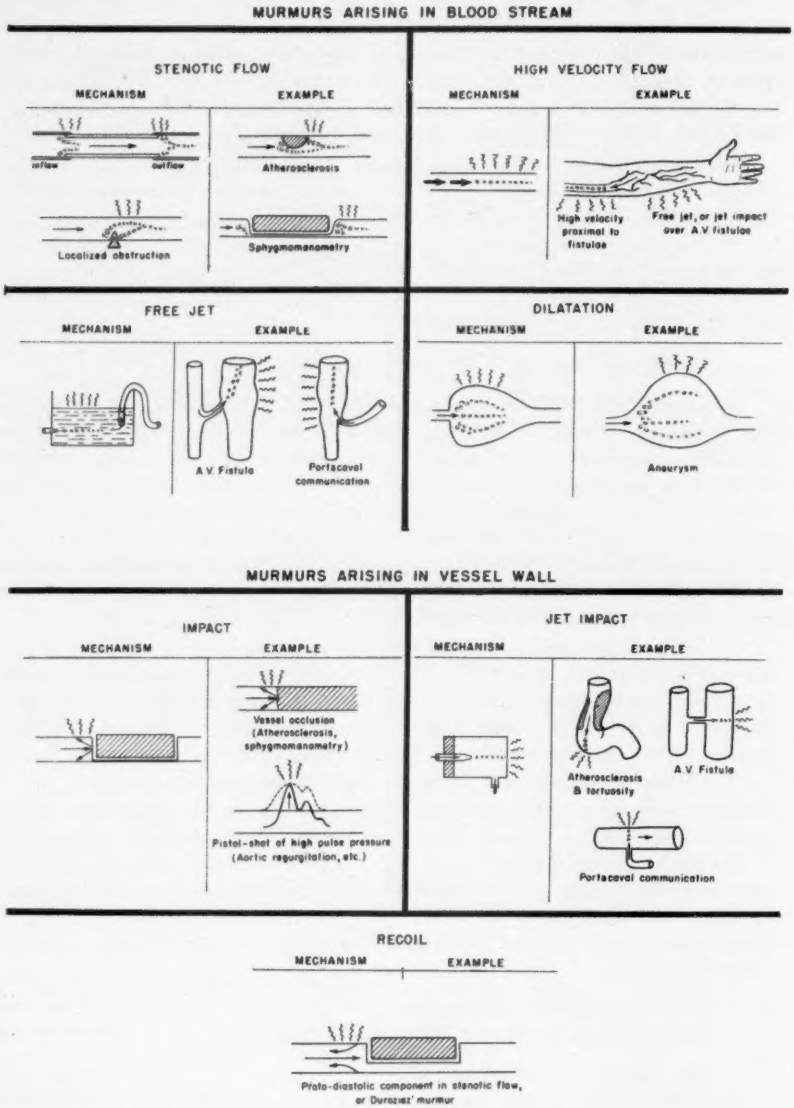


Fig. 1.—Mechanisms producing murmurs in the blood stream and in the vessel wall.

audible beyond 78% obstruction. The phase relationships of the murmur were also of interest. At low levels of obstruction the murmur occurred as a late systolic crescendo. As the stenosis was increased, it began earlier in systole and was continued as a diastolic decrescendo.

It should be emphasized that in order to produce vibrations, a change in vessel size must be abrupt, since a gradual convergence or divergence of the vessel wall tends to overcome turbulence.[2] A localized area of obstruction in the presence of low velocity may likewise fail to give rise to sound production if the obstruction is gradual on its proximal, and abrupt on its distal, face. Under these conditions a vortex may form distal to the obstruction but may simply rotate here without setting up a widespread disturbance.[2] With an increase in pressure and velocity a bruit may be produced.

When a vessel receives blood greater in volume and under a higher pressure than that to which it is accustomed, it becomes distended close to its elastic limit.

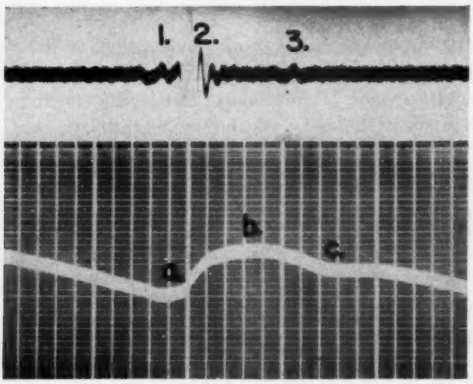


Fig. 2.—Analysis of a single Korotkoff sound (upper) recorded below compressing cuff and correlated with pulse pressure tracing (lower) from same level. *1, 2,* and *3* are impact, stenotic flow, and recoil components; *a* and *b* denote beginning and crest of systolic limb, and *c*, dicrotic notch. Paper speed was 75 mm. per second.

Under these conditions, a more or less continuous "high velocity" flow is attained, and a fairly continuous murmur may be produced. This may explain the murmurs heard over veins far proximal to the entrance of an arteriovenous fistula or of a large portacaval communication or over the arterial collaterals in coarctation of the aorta.

Vibrations Arising in the Vessel Wall.—The arterial wall is subject to sudden changes in pressure at the beginning of systole and diastole which may cause it to vibrate. These vibrations are ordinarily inaudible, but with a high pulse pressure and in the presence of some vessel lesions they may be sufficiently augmented to cause brief "sounds" and finally audible murmurs.

Both these protosystolic and protodiastolic murmurs, which we term "impact" and "recoil," contain some vibrations that have their origin in the aortic valve.[7]

7. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, Am. Heart J. **23**:591, 1942.

As regards the impact murmur, the earliest portion (Fig. 2) appears to consist of sound vibrations set up by the opening of the aortic valve, which arrive in the artery prior to those produced by the rise of the systolic limb of the pulse wave. The earliest recoil vibrations again correspond to the sound produced by the closure of the valve, which arrives prior to the beginning of the dicrotic notch of diastole. When the normal reversal of blood flow [8] and indrawing of the vessel wall, which occurs at the time of the dicrotic notch, are exaggerated, additional vibrations are added to those of aortic valve origin.[9] Conditions increasing the depth of the dicrotic notch, such as aortic insufficiency, augment these vibrations and cause an audible diastolic murmur. This murmur is further increased by moderate narrowing of the vessel.[9]

A further mechanism for vessel wall vibration, the "jet impact," exists when the jet of blood emerging from a narrowed vessel segment is so oriented as to strike a portion of the distal vessel wall.

MURMURS PRODUCED BY EXPERIMENTAL ARTERIAL COMPRESSION

Murmur formation by pneumatic cuff compression of the brachial artery of normal subjects was studied in order to explain the clinically encountered murmurs caused by vessel obstruction. In these experiments, the effects of the vessel occlusion was studied proximal to, and immediately beneath, the cuff, as well as distal to it.

Apparatus and Method.—Most of the observations were made with the sphygmomanometric apparatus described by Rappaport and Luisada [10] and supplied through the kindness of Mr. Rappaport. The cuff of this apparatus contains two pneumatic chambers, one of which compresses the arm at any desired pressure. The second is connected to two piezoelectric transducers, one reacting to the sound vibrations, the other to the pressure variations of the pulse wave. The output of the first is fed into the phonocardiographic, the second into the electrocardiographic, channels of the electrocardiograph, allowing a simultaneous registration of both sound and pulse wave.

Registration of the effects distal to compression was made by applying the cuff with the pressure chamber proximal and the registration cuff distal. The effects proximal to compression were then recorded by turning the cuff so that the registration chamber was proximal.

Study of the sound over the compressed segment proper was accomplished by placing the microphone of the Maico Stethetron device beneath the cuff of an ordinary sphygmomanometer in such a way that the microphone compressed the artery while it picked up the sound. For purposes of comparison, the sounds above and below the cuff were again registered with the same apparatus.

Results.—A. Effects Distal to the Compression (Figs. 2 and 3): Figure 2 shows the fully developed Korotkoff sound distal to the cuff inflated to mid-systolic pressure. The sound is seen to comprise three distinct components: a few vibrations of low frequency and amplitude starting just before the systolic pulse phase; a larger group of vibrations of higher frequency and amplitude, in early systole, and arranged in a crescendo-decrescendo form, with dominance of

8. Shipley, R. E.; Gregg, D. E., and Schroeder, E. J.: An Experimental Study of Flow Patterns in Various Peripheral Arteries, Am. J. Physiol. **138**:718, 1943.

9. Luisada, A. A.: On the Pathogenesis of the Signs of Traube and Duroziez in Aortic Insufficiency: A Graphic Study, Am. Heart J. **26**:721, 1943.

10. Rappaport, M. B., and Luisada, A. A.: Indirect Sphygmomanometry, J. Lab. & Clin. Med. **29**:638, 1944.

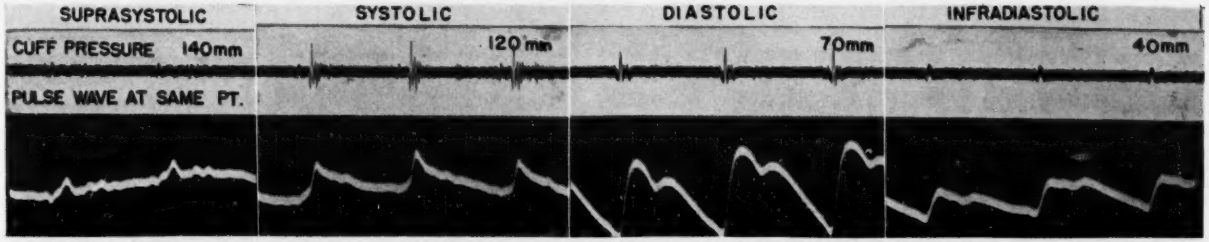


Fig. 3.—Arterial sounds in sphygmomanometry. Sounds distal to the compressing cuff. Impact and recoil vibrations are present at all pressures shown. When cuff pressure is above systolic level, they are transmitted from artery above. Stenotic flow vibrations are present at systolic and diastolic pressure levels. Paper speed is 25 mm. per second.

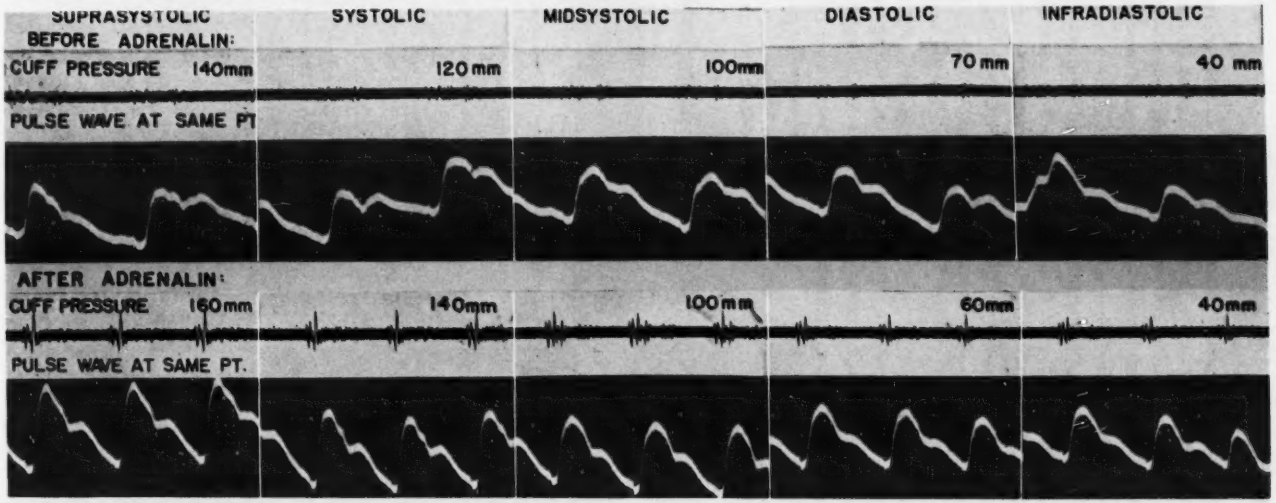


Fig. 4.—Sounds recorded proximal to experimental arterial compression. In upper curves, with subject at rest, note small impact and recoil vibrations at all pressures shown, with minor stenotic flow vibrations at systolic pressures. With epinephrine (adrenalin®) administration, impact and recoil vibrations are intensified and prolonged. The few stenotic flow vibrations are also more pronounced.

the decrescendo part, and a third group of a few vibrations of low frequency and amplitude in the protodiastolic phase, just prior to the dicrotic notch. The tentative assumption was made that the first component represents impact, the second, stenotic flow, and the third, recoil, in the sense in which the terms were discussed in the preceding section.

B. Effects Proximal to the Compression (Fig. 4): Figure 4 records the vibrations proximal to the compressing cuff, with the subject both at rest and after epinephrine administration. In the curves prior to epinephrine administration (pulse pressure, 50 mm. of mercury), the impact and recoil vibrations are detectable at all the cuff pressures, about equally marked when compression is above or at systolic levels, but less marked at diastolic and infradiastolic levels, when the pulse wave meets but little hindrance to its passage. These curves differ from those taken below the cuff (Fig. 4) in the prolongation of the impact and recoil vibrations and the absence of the stenotic flow vibrations.

With the pulse pressure increased to 80 mm. of mercury by epinephrine, more energy is imparted to the pulse wave. The impact vibrations especially are increased in amplitude and duration, with a slight increase in frequency. They are

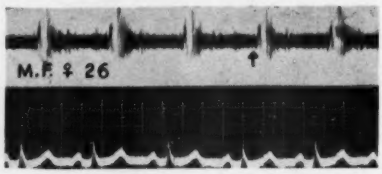


Fig. 5.—Sound tracing directly at an area of experimental arterial constriction with application of cuff on left arm in a normal subject. All three components are intense and prolonged. Impact and stenotic flow vibrations combine to form a crescendo-decrescendo ("diamond-shaped") murmur. Arrow indicates calculated moment of arrival of pulse wave. Subject's blood pressure was 120/80. Tracing was recorded at pressure of 115 mm. Hg.

greatest when the artery is almost totally occluded and are arranged in a crescendo occupying most of the early systolic phase. The vibrations gradually diminish as the cuff pressure falls, but they are still present, along with the recoil component, at infradiastolic levels. A few vibrations in midsystole, seen at the midsystolic pressure level, probably represent proximal transmission of stenotic flow vibrations.

C. Effects in the Compressed Segment (Fig. 5): The tracing made directly from the compressed segment is characterized, especially at high degrees of obstruction, by the presence of loud vibrations of long duration. The impact component is intense and blends with a loud stenotic flow component to form a crescendo-decrescendo murmur which lasts almost to the time of the marked recoil vibrations.

Deductions.—Certain deductions may be drawn from the above and applied to the analysis of murmurs observed in the presence of pathological obstruction of the arteries:

1. A murmur is observed distal to partial arterial obstruction, consisting of three components: impact, occurring in the protosystolic pulse phase; stenotic flow,

starting a little later in early systole, and recoil, occurring in the protodiastolic phase. Only the stenotic flow vibrations are ordinarily of significant amplitude. They are arranged in a crescendo-decrescendo form, with decrescendo dominance. All three components may be blended when the pulse pressure is high.

2. The murmur heard directly over a narrowed segment of artery is loud and of long duration, representing a blending of the impact and stenotic flow components into a crescendo-decrescendo form. The blending in this location is apt to occur even at low pulse pressures.

This murmur is reminiscent of the "diamond-shaped" murmur heard over a stenotic pulmonic or aortic valve and of a similar murmur heard over a coarctation of the aorta.[11]

3. Both impact and recoil are present proximal to an obstruction, but the vibrations are usually feeble. A high pulse pressure increases the amplitude, duration, and frequency of both components, especially the impact, which gives rise to a crescendo murmur. Some loud stenotic flow vibrations may be transmitted proximally when the obstruction is incomplete.

CLINICAL OBSERVATIONS

Disorders of the Arteries.—A. Narrowing by External Pressure: It is apparent that compression of an artery by a neighboring structure can engender a murmur. Sound production in sphygmomanometry (Fig. 3) has already been described. Other examples encountered during this study include the factitious murmur (Fig. 6 [upper]) produced by excessive pressure of the stethoscope, compression of the external iliac artery by lymph nodes in lymphatic leukemia, and partial obstruction of the common iliac artery by a displaced bone fragment in a fractured pelvis.

In many patients with cervical rib or the scalenus syndrome, the subclavian artery is compressed as it passes across the cervical or first thoracic rib. The compression is often demonstrable only on performing the so-called scalenus maneuver, in which the scalenus muscle is tensed while the patient takes a deep inspiration and the examiner pulls down on the homolateral arm. The arterial compression is usually appreciated by finding a diminution of the radial pulse by palpation. As in sphygmomanometry, auscultation distal to the compression, i. e., over the subclavian artery in the posterior cervical region, is a more sensitive procedure.[12] The systolic murmur heard (Fig. 6 [lower]) is quite comparable with the Korotkoff sound.

B. Intrinsic Obstruction: The experimental study cited above demonstrated that murmurs of great amplitude may be heard directly over an area of incomplete obstruction. Arteriosclerosis is the disease par excellence in which obstruction and murmur formation may thus be encountered. The roughness of the wall and the

11. (*a*) Wells, B. G.; Rappaport, M. B., and Sprague, H. B.: The Sounds and Murmurs in Coarctation of the Aorta, Am. Heart J. **38**:69, 1949. (*b*) Levine, S. A., and Harvey, P.: Clinical Auscultation of the Heart, Philadelphia, W. B. Saunders Company, 1949.

12. Edwards, E. A., and Levine, H. D.: Auscultation in the Diagnosis of Compression of the Subclavian Artery, New England J. Med. **247**:79, 1952.

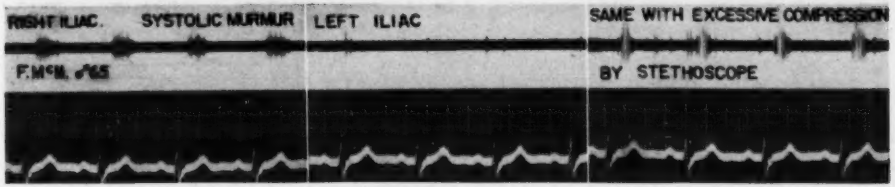
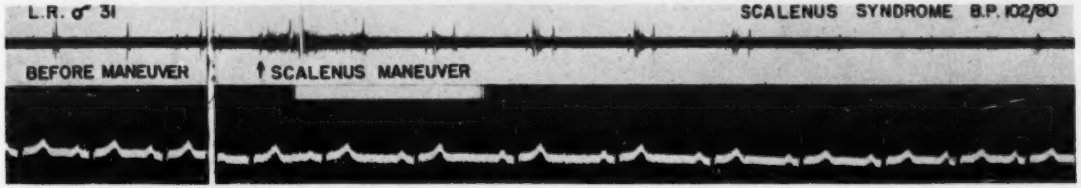


Fig. 6.—Upper, factitious murmur of crescendo-decrescendo form produced by pressure with stethoscope over left iliac artery. Murmur in right iliac artery is due to arteriosclerotic narrowing. With high pulse pressure, impact and stenotic flow components blend into a long duration murmur. Subject's blood pressure was 170/90.



Lower, auscultation over distal part of subclavian artery in patient with scalenus syndrome. At rest, the two heart sounds are noted. Performing scalenus maneuver introduces stenotic [12] flow vibrations, but almost all sound disappears with more complete occlusion.

eccentric situation of atheromata are peculiarly suitable for the production of the necessary turbulence. The frequency of murmurs in arteriosclerotic vessels in general was noted by Sahli,[1] and more recently has been emphasized for the aorta by Hiestand and Morris [13] and by Popkin.[14] In the present investigation murmurs

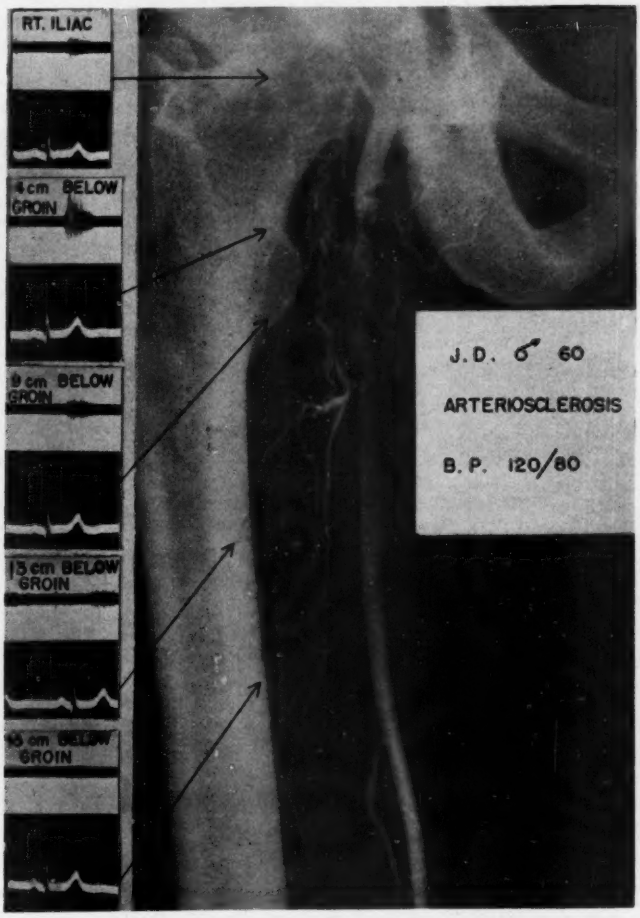


Fig. 7.—Sound and roentgen arteriogram in arteriosclerosis. Murmur is loudest at area of greatest narrowing. It is systolic and mainly decrescendo in form, impact and recoil being minimal at this low pulse pressure.

13. Hiestand, R. F., and Morris, R. L.: Note on the Transmission of Aortic Systolic Murmurs to the Abdominal Aorta, Am. Heart J. **8**:249, 1932.

14. Popkin, R. J.: A Systolic Murmur Heard over the Lower Abdominal Aorta: Its Significance in Peripheral Vascular Diseases, Angiology **1**:244, 1950.

were detected, occasionally accompanied with palpable thrills, in about one-half of the patients with this disease. The murmurs are usually audible over the femoral or iliac arteries. Occasionally one is heard along the entire course of the major artery, from iliac to popliteal level. Those originating in the terminal aorta may be heard above and to the left of the umbilicus or occasionally over the lumbar spine. Roentgen arteriography has demonstrated that the murmurs are indeed of greatest intensity directly over areas of incomplete obstruction, with a diminishing audibility above and below the obstruction (Figs. 7 and 9).

The murmur is systolic and gruff in character. When the pulse pressure is low, registration shows the sound to consist mainly of a stenotic flow component, with a prolonged decrescendo limb (Figs. 7 and 8). Above the obstruction the impact component may be more prominent (Fig. 7, "iliac"). A high pulse pressure, with or without hypertension, intensifies the impact and prolongs the stenotic flow

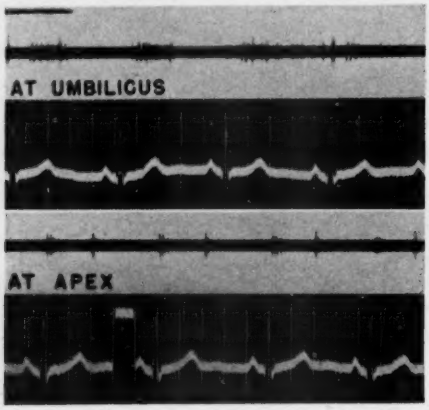


Fig. 8.—Arteriosclerotic murmur in aorta of a normotensive woman (S. B., aged 47, with blood pressure of 120/80), showing three distinct components. Disparity from sounds at cardiac apex (lower) is noted. Patient has stenosis of aorta or iliac arteries.

component, producing a typical blended crescendo-decrescendo murmur at the site of obstruction (Figs. 6 [upper], 9, and 10). Below the obstruction, each of the three components may be distinct (Fig. 10, "rt. groin").

Certain deductions may be drawn regarding murmur production in arteriosclerotic obstruction: 1. The presence of a murmur over a vessel indicates some patency, since no murmurs were heard either proximal or distal to complete obstruction. In some patients other evidence of the development of complete obstruction coincided with the disappearance of a previously audible systolic murmur. Theoretically, one might encounter a murmur proximal to a complete occlusion if the pulse pressure were extremely high, but we have not observed it clinically. 2. A very loud murmur indicates a considerable degree of obstruction or the concomitance of a smaller obstruction and a high pulse pressure. 3. A murmur of long duration usually depends upon the combination of much narrowing and a high pulse pressure.

No murmurs have been encountered in arteries affected by thromboangiitis obliterans or occluded by thrombosis. A short impact murmur has been heard proximal to an embolus in one hypertensive patient. These diseases differ from arteriosclerosis in the more abrupt and complete obstruction they produce. They therefore do not afford the proper conditions for stenotic flow vibrations.

Segmental spasm of an artery may give rise to murmur formation, judging by the observation of palpable thrills at the site of embolectomy. Such thrills have disappeared in a minute or two as the vessel has relaxed.

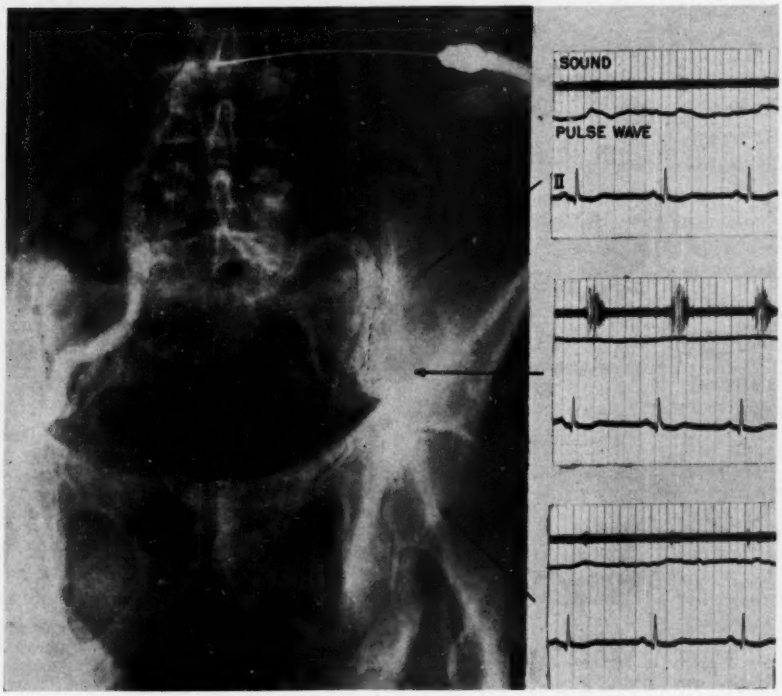


Fig. 9.—Sound and roentgen arteriogram in arteriosclerosis (Patient W. H., a man aged 65, with blood pressure of 142/60). With high pulse pressure, loud blended crescendo-decrescendo murmur is produced.

C. Aneurysm: The systolic murmur over an arterial aneurysm is probably the most widely appreciated of peripheral vascular murmurs. While several examples were observed during the present investigation, none was satisfactorily studied graphically. The sounds over aortic aneurysms are complicated by the heart sounds and murmurs, and murmurs over peripheral aneurysms are apt to be very faint. The low intensity of sound over the peripheral aneurysms may be accounted for, at least in part, by the fusiform nature of many of these enlargements and by the poor transmissibility of their usual lining of parietal thrombus. Dissecting aneurysms

may give rise to systolic murmurs. An example of a systolic murmur of long duration over such a lesion has been shown by Levine and Harvey.[11b]

Arteriovenous Fistula.—It is well known that a continuous murmur is heard over an arteriovenous fistula (Fig. 11). It may be caused by a free jet or jet-impact mechanism. The present study has emphasized certain aspects of the pulse phase and location of this murmur [15]:

1. Though the murmur is continuous, the usual systolic accentuation may be so marked as to create a murmur which may impress one as purely systolic. Even when the murmur is classic, compression of the outgoing vein changes the murmur

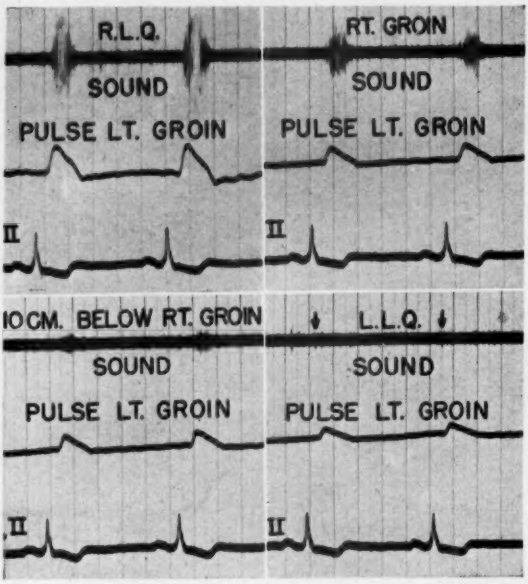


Fig. 10.—Murmur in arteriosclerosis and hypertension (Patient T. M., a man aged 76, with blood pressure of 178/84 and pulse pressure of 94 mm.). Both femoral pulsations were present, but a crescendo-decrescendo murmur was heard only over right iliac and femoral arteries. Slight impact vibrations denoted by arrows are present over left iliac artery. Same amplification was used throughout.

into a systolic one. The explanation for this phenomenon lies in changes in the pressure gradient at the fistula. When a fistula leads into an unobstructed vein, the gradient from artery to vein is adequate for rapid flow and murmur formation both during systole and during diastole. The murmur is, therefore, continuous, although the rise in pressure and velocity during systole creates an accentuation during that phase. Compression of the outgoing vein raises the venous pressure to near-diastolic levels, so that an adequate pressure gradient for rapid flow exists

15. Edwards, E. A., and Levine, H. D.: The Murmur of Arteriovenous Fistula, New England J. Med., to be published.

only during systole. An identical explanation of the occasional systolic nature of the murmur in patent ductus arteriosus has been offered by Burchell [16] and by Myers and associates.[17]

2. Murmur formation is not limited to the site of the fistula but exists over long stretches of the vein central to the entrance of the fistula (Fig. 11), sometimes reaching all the way back to the heart. The murmur heard proximally is even more continuous than that heard over the site of the fistula. The accentuation in systole is less marked and occurs somewhat later in this phase of the pulse. These differences of the murmur in the two sites suggest that the proximal murmur is partly transmitted from the fistula proper and partly generated in the vein, possibly from the mechanism previously alluded to as high velocity flow.

The existence of a murmur proximal to a fistula is of great importance in the localization of fistulae, especially in cases of congenital origin, in which multiple fistulae are the rule. In such patients one may determine the location of the proximal fistula by compressing distal areas of the limb, while listening for obliteration of the murmur in a proximal segment of the vein.

Disorders of the Veins.—Murmurs are heard much less frequently in veins than in arteries, owing presumably to the usual low velocity of the venous stream. The murmurs encountered during the present study include the hum over the internal jugular vein of children (Fig. 12) and the murmur proximal to the entrance of a porta-systemic communication (Fig. 13) and of an arteriovenous fistula (Fig. 11). The jugular hum is probably caused by narrowing of a vein in which the velocity is already high. The murmur over the veins proximal to the portal communication may be due partly to free jet flow or jet impact and partly to high velocity flow. The venous murmur proximal to arteriovenous fistula has been considered above.

The hum often heard over the great veins of the neck has been known for more than a century.[18] It occurs so frequently in children under 15 years of age as to be accounted of no significance by most clinicians. Though the murmur is continuous, its intensification by certain maneuvers and its diastolic accentuation suggest that narrowing of the lumen is significant in its causation. Most commonly the murmur is heard over the internal jugular vein, with the patient sitting or standing, and during deep inspiration. In this position gravity greatly increases the velocity of flow in the vein, and this is aided by the inspiratory lowering of intrathoracic pressure. The diastolic accentuation is a further indication of an increased pressure gradient and flow, since auricular pressure is lowest in this phase (Fig. 12).

The role of narrowing of the lumen is suggested by the intensification of the murmur on turning the head to one side, since the vein is thus put on the stretch and distorted by the structures about it. Enlarged lymph nodes are occasionally

16. Burchell, H. B.: Variations in the Clinical and Pathologic Picture of Patent Ductus Arteriosus, M. Clin. North America **32**:911, 1948.

17. Myers, G. S.; Scannnell, J. G.; Wyman, S. M.; Grey-Dimond, E., and Hurst, J. W.: A Typical Patent Ductus Arteriosus with Absence of the Usual Aortic Pulmonary Pressure Gradient and of the Characteristic Murmur, Am. Heart J. **41**:819, 1951.

18. Landis, H. R. M., and Kaufman, I.: The Occurrence of Venous Hums in Children, Arch. Pediat. **29**:88, 1912.

clearly responsible for the narrowing of the lumen, and the possibility that such pathology is generally present is at least suggested by finding the murmur at a time of life when node enlargement is common.

A well-documented instance of venous hum heard over the veins of the abdomen distal to the entrance of a large porta-systemic communication was published by Pégot in 1833 [19] and Cruveilhier in 1835.[20] In 1942, Armstrong and his associates collected 55 reported cases of this so-called Cruveilhier-Baumgarten syndrome.[21] We have studied a patient with this syndrome at the Boston City Hospital, through the kindness of Dr. F. Biguria.[22] Moderately enlarged periumbilical veins were present, with obvious flow upward to the xiphoidal region and downward to the saphenous veins, especially the right. A murmur was heard over the enlarged veins, with two points of maximal intensity, one in the epigastrium,

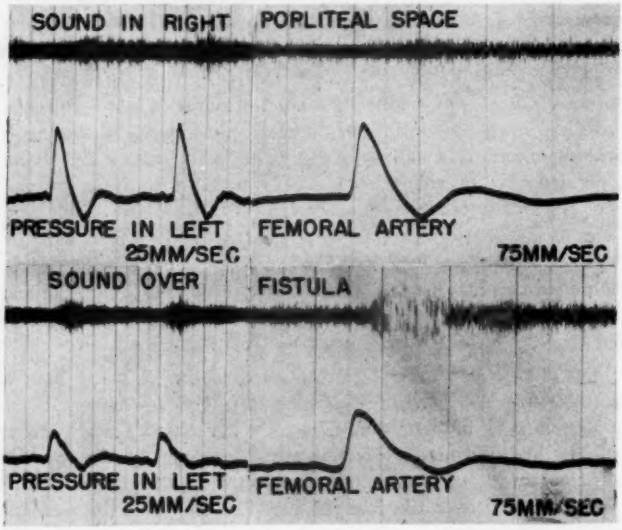


Fig. 11.—Continuous murmur over arteriovenous fistula of right posterior tibial vessels, below, and over effluent vein, above, in Patient D. N., a man 21 years of age. Paper speeds are as noted. Standardization of upper pair of pressure curves was not identical with that of lower pair.

the other just below and to the right of the umbilicus. The murmur was continuous and high-pitched (Fig. 13). It was subject to sudden increases in intensity and

19. Pégot, M.: Tumeur variqueuse avec anomalie du système veineux et persistance de la veine ombilicale: Développement des veines sous-cutanées abdominales, Bull. Soc. anat. Paris **8**:49, 1833.

20. Cruveilhier, J.: Anatomie pathologique du corps humain, Paris, J.-B. Ballière, 1829-1835, Vol. 1, Part 16, plate 6.

21. Armstrong, E. L.; Adams, W. L.; Tragerman, L. J., and Townsend, E. W.: The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of 2 Additional Cases, Ann. Int. Med. **16**:113, 1942.

22. Altman, G. E.; Victor, M.; Kramer, G., and Marks, A.: The Cruveilhier Syndrome: Report of a Case and Survey of the Literature, to be published.

pitch, suggesting the screaming of a high wind. These increases did not coincide with any phase of the pulse or respiratory cycle. Possibly it was caused by a changing position of the falciform ligament and its contained vessels in response to movement of the intestine. Compression of the veins leaving the areas of maximal intensity diminished the intensity and pitch of the murmur at the corresponding maximal point.

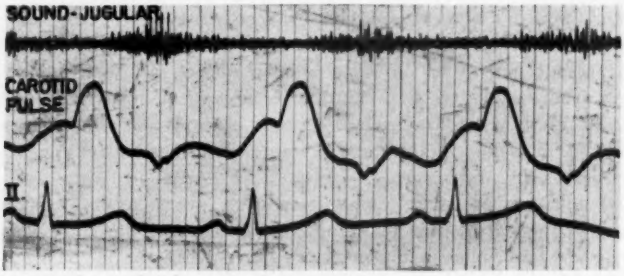


Fig. 12.—Jugular venous hum in a boy (M. F., aged 8 years) with lymphadenitis (submaxillary node mass). Note diastolic accentuation. Paper speed was 75 mm. per second.

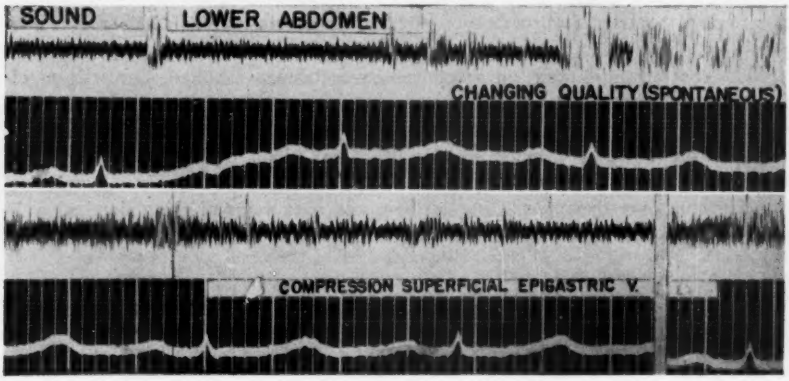


Fig. 13.—Continuous hum over superficial veins in portal obstruction (Patient T. O'B., a man aged 38, Cruveilhier-Baumgarten syndrome). Compression of outgoing vein reduces intensity and frequency (pitch) of murmur.

Many authors have suggested that venous hums may be found among cases of portal obstruction much oftener than suggested by the paucity of reported cases.[23] Auscultation should be carried out over all the abdomen since large deep-lying anastomoses, especially those between the splenic and left renal veins, may thus be recognized.[24]

23. Bloom, H. J. G.: Venous Hums in Hepatic Cirrhosis, Brit. Heart J. **12**:343, 1950.

24. Edwards, E. A.: Functional Anatomy of the Porta-Systemic Communications, A. M. A. Arch. Int. Med. **88**:137, 1951.

SUMMARY

This is a study of murmurs generated within the peripheral blood vessels in a variety of disorders. The murmurs are presented as registered by phonocardiographic apparatus, and correlation is made with roentgen visualization of the vessels.

A classification of the mechanisms of murmur formation is offered, based partly on the work of Sahli and of Bondi.

Murmur production at an area of narrowing was studied by compression of the brachial artery in normal persons. Murmurs at, or distal to, the site of compression consist of three components: an early systolic impact, a later systolic stenotic flow, and a protodiastolic recoil. A murmur consisting of impact and recoil, with an occasional trace of the transmitted stenotic flow, is discernible proximal to the obstruction. Elevation of the pulse pressure intensifies and prolongs all three components, especially the impact.

Arterial murmurs are mainly systolic in time, owing to the existence of a high pressure gradient at this pulse phase. Elements of the three components mentioned above are noted in the murmurs heard when the lumen is narrowed, whether by external pressure as with cervical rib or in the scalenus maneuver, or in intrinsic obstruction as by arteriosclerosis. A gruff systolic murmur was heard over the aorta or over the iliac or femoral arteries in about half of all patients with arteriosclerosis. No murmurs were heard in thromboangiitis obliterans or proximal to arterial thrombosis. Arterial aneurysms often failed to give the classic systolic murmur, probably because of parietal thrombosis.

The continuous murmur of arteriovenous fistula was studied. Constriction of the effluent vein converted such a murmur to a systolic one by eliminating the necessary gradient for a critical velocity in the diastolic phase. A murmur, probably due to high velocity flow, is heard far along the vein proximal to a fistula.

Murmurs over the internal jugular vein and over veins of the abdominal wall in portal obstruction are also demonstrated.

ANTIBIOTIC SYNERGISM AND ANTAGONISM

Review of Experimental Evidence

ERNEST JAWETZ, M.D., Ph.D.
SAN FRANCISCO

THE INTRODUCTION of antibiotics into clinical medicine about a decade ago has revolutionized medical practice. These invaluable agents are now among the most commonly used drugs. It has been estimated that in 1948 the production of penicillin approached 62 tons,[1] and it may be suspected that about 5% of this quantity was used on proper clinical indication. The large-scale, indiscriminate use of antibiotics may well be associated with the increasing incidence of drug-fast infections which fail to respond to therapy with any single antibiotic, even when it is employed in very large doses. This type of clinical problem is illustrated in the following case (Fig. 1).

REPORT OF A CASE

A 38-year-old housewife, with a history of rheumatic fever in childhood, consulted a physician because of amenorrhea for two months. The physician found her pregnant and, because of a loud systolic murmur, recommended a therapeutic abortion, which was performed in April, 1948. A few days after the operation the patient had fever and malaise, for which she received sulfonamides. There was little improvement, and subsequently nodules in the fingertips, petechiae, splinter hemorrhages, marked fatigue, and weight loss developed. These symptoms and signs were not significantly influenced by short courses of penicillin, streptomycin, and various sulfonamides.

When the patient entered the University of California Hospital on Aug. 10, 1948, she presented all stigmata of subacute bacterial endocarditis, with splenomegaly and a loud rough systolic murmur over the entire precordium, maximally heard in the mitral area. There was no diastolic murmur, and her blood pressure was 130/70. She showed mild clubbing of the fingers.

Laboratory examinations revealed the following: The hemoglobin concentration was 12 gm. per 100 ml. Red blood cells numbered 4,450,000 and white blood cells 5,700, with normal distribution. Her urine contained occasional red blood cells and white blood cells, but no protein. Repeated blood cultures yielded Streptococcus faecalis, inhibited in the test tube by penicillin, 8 units per milliliter.

The patient received a course of penicillin, 10,000,000 units daily, for 33 days in August to September, 1948. During treatment she felt much improved, but bacteriological relapse was

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The Almroth Wright Lecture delivered on June 10, 1952, at St. Mary's Hospital Medical School, London.

From the Divisions of Microbiology, Medicine, and Pediatrics, University of California School of Medicine, San Francisco.

This study is based on experimental work performed by a group including the following: J. A. Bruff, V. R. Coleman, J. B. Gunnison, E. Jawetz, C. Miles, R. S. Speck, and M. C. Shevky. The work was supported, in part, by grants from the Committee on Research, University of California School of Medicine, San Francisco. H. D. Brainerd, J. E. Eiler, L. Goldman, and others offered valuable advice.

1. Reiman, H. A.: Infectious Diseases, A. M. A. Arch. Int. Med. **87**:128-174, 1951.

evident soon after therapy was discontinued. This sequence repeated itself with courses of aureomycin (total of 180 gm. in 32 days), penicillin (total 3,000,000,000 units, or 1,800 gm., of crystalline penicillin G in 30 days), and combined administration of dihydrostreptomycin, penicillin, sulfonamides, and chloramphenicol, given in desperate attempts to cure this infection. During her treatment with penicillin, blood levels repeatedly reached 1,000 units per milliliter. Five months after the last course of therapy hemiplegia developed, and the patient died 17 days later, on Dec. 7, 1949. Blood cultures during the last months of life had yielded Str. faecalis, 300 to 400 colonies per milliliter of blood, apparently inhibited by penicillin, 10 to 20 units per milliliter.

EXPERIMENTAL STUDIES

The manifest failure to cure this patient stimulated us to undertake an investigation into the effects of drug combinations on micro-organisms. Others had suggested [2] that adding one antimicrobial agent to another might result in either increased or decreased effectiveness. Because of our conviction that the killing of micro-organisms, rather than their inhibition, was an essential requirement for curative action of a drug in bacterial endocarditis,[3] we selected the rate of bacteri-

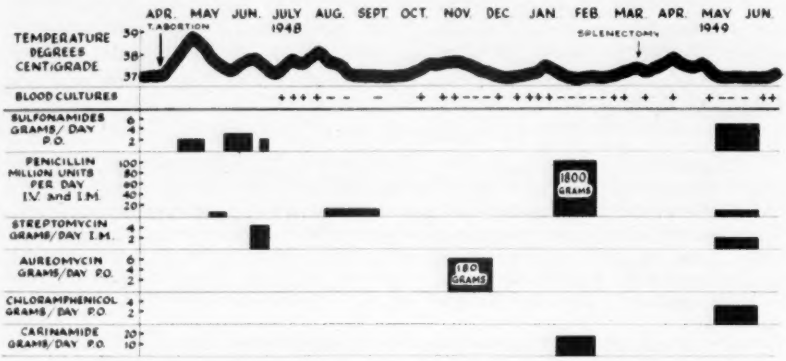

Fig. 1.—Clinical course of patient V. W., a 38-year-old woman with bacterial endocarditis (Enterococcus) after therapeutic abortion. Patient died on Dec. 7, 1949.

cidal action as our principal criterion for drug action in the test tube. Experiments with a fecal Streptococcus yielded the following principal results (Fig. 2): Penicillin alone gave a certain optimal bactericidal rate but permitted the survival of significant numbers of bacteria. The addition to this optimal concentration of penicillin of an amount of streptomycin which, alone, appeared to be without any effect resulted in a striking increase in the rate of bactericidal action and death of

2. Hobby, G. L., and Dawson, M. H.: The Effect of Sulfonamides on the Action of Penicillin, J. Bact. **51**:447-455, 1946. Klein, M., and Kalter, S. S.: The Combined Action of Penicillin and the Sulfonamides in Vitro, ibid. **51**:95-105, 1946. Lankford, C. E., and Lacy, H.: In Vitro Responses of Staphylococcus to Aureomycin, Streptomycin and Penicillin, Texas Rep. Biol. & Med. **7**:111-124, 1949. Bigger, J. W.: Synergism and Antagonism as Displayed by Certain Antibacterial Substances, Lancet **2**:46-57, 1950. Price, C. W.; Randall, W. A.; Welch, H., and Chandler, V. L.: Studies of the Combined Action of Antibiotics and Sulfonamides, Am. J. Pub. Health **39**:340-344, 1949.

3. Hunter, T. H.: Speculations on the Mechanism of Cure of Bacterial Endocarditis. J. A. M. A. **144**:524-527, 1950.

all exposed micro-organisms. This phenomenon we labeled synergism. On the other hand, the addition of chloramphenicol in a barely bacteriostatic concentration to the same optimal amount of penicillin had the opposite effect. The rate of bactericidal action was greatly decreased, so that in 24 hours more bacteria survived than with penicillin alone. We applied the term antagonism to that effect. It is proposed to describe here the areas in which these phenomena have been encountered and to summarize studies designed to elucidate their mode of action.

THE OCCURRENCE OF ANTIBIOTIC ANTAGONISM AND SYNERGISM

Test-tube experiments indicated that antagonism between a number of antimicrobial substances was common. In addition to the pair mentioned earlier, it

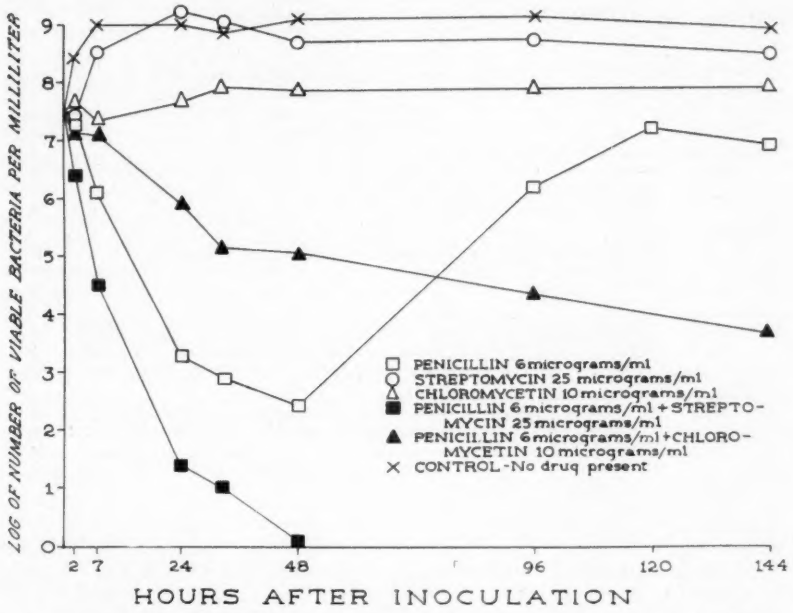

Fig. 2.—Effect of penicillin (6 γ per milliliter), streptomycin (25 γ per milliliter), and chloramphenicol (chloromycetin®; 10 γ per milliliter) alone and in combination on a strain of Str. faecalis in vitro. (From Jawetz and others[4a])

was found that aureomycin, chloramphenicol, and terramycin were all capable of interfering with the action of penicillin, streptomycin, or bacitracin on a variety of Gram-positive and Gram-negative micro-organisms.[4] Under certain conditions sul-

4. (*a*) Jawetz, E.; Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254-256, 1950. (*b*) Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900-911, 1950. (*c*) Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin, A. M. A. Arch. Int. Med. **87**:

(Footnote continued on next page)

fonamides were similarly antagonistic.[5] That this might be only an in vitro phenomenon was soon disproved by the demonstration that in certain experimental infections of mice more animals succumbed with the simultaneous administration of two drugs than with administration of a single drug. This occurred with several drug schedules, as illustrated in Table 1.[4c-e] The rather stringent experimental conditions, discussed later, that were necessary to elicit antibiotic antagonism in vivo suggested that it would be observed but rarely in the treatment of human disease. However, the possibility of its occurrence in clinical practice was emphasized by Lepper and Dowling in their study on pneumococcic meningitis.[6] Among entirely comparable groups of patients the mortality was 30% in those treated with penicillin alone but 79% in those who received aureomycin in addition to penicillin. Others have likewise suspected the occurrence of antibiotic antagonism in clinical situations[7] but further conclusive proof has not appeared.

TABLE 1.—*Examples of Antibiotic Antagonism in Experimental Infections of Mice*

Infection	Drug and Dosage Schedule	Per Cent Cure*
Streptococcus (acute)	None	0
	Penicillin, 30 γ 1 hr. after infection	96
	Chloramphenicol, 50 γ 1 hr. after infection	19
	Penicillin + chloramphenicol	35
Klebsiella	None	4
	Penicillin, 6 mg. 1 hr. after infection	82
	Aureomycin, 10 γ 1 hr. after infection	8
	Penicillin + aureomycin	33
Streptococcus (acute)	None	0
	Streptomycin, 300 γ in 3 doses at 4-hr. intervals, beginning 1 hr. after infection	56
	Chloramphenicol, 30 γ in 3 doses at 4-hr. intervals, beginning 1 hr. after infection	8
	Streptomycin + chloramphenicol	18
Streptococcus (subacute)	None	0
	Penicillin, 180 γ 5 times at 24-hr. intervals, beginning 24 hr. after infection	100
	Terramycin, 15 γ 5 times at 24-hr. intervals, beginning 24 hr. after infection	16
	Penicillin + terramycin	42

* Based on groups of 20 to 60 mice each.

349-359, 1951. (*d*) Speck, R. S.; Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism: The Interference of Aureomycin or Terramycin with the Action of Penicillin in Infections in Mice, ibid. **88**:168-174, 1951. (*e*) Jawetz, E.; Gunnison, J. B., and Speck, R. S.: Studies on Antibiotic Synergism and Antagonism: The Interference of Aureomycin, Chloramphenicol and Terramycin with the Action of Streptomycin, Am. J. M. Sc. **222**:404-412, 1951. (*f*) Jawetz, E.; Gunnison, J. B.; Bruff, J. A., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: Synergism Among 7 Antibiotics Against Various Bacteria in Vitro, J. Bact., to be published.

5. Gunnison, J. B.; Speck, R. S.; Jawetz, E., and Bruff, J. A.: Studies on Antibiotic Synergism and Antagonism: The Effect of Sulfadiazine on the Action of Penicillin in Vitro and in Vivo, Antibiotics & Chemother. **1**:259-266, 1951.

6. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin Plus Aureomycin, A. M. A. Arch. Int. Med. **88**:489-494, 1951.

7. (*a*) Cates, J. E.; Christie, R. V., and Garrod, L. P.: Penicillin-Resistant Subacute Bacterial Endocarditis Treated by a Combination of Penicillin and Streptomycin, Brit. M. J. **1**:653-656, 1951. (*b*) Rutenburg, A. M.; Jacob, S. W.; Schweinburg, F. B., and Fine, J.: Aureomycin in the Treatment of Diffuse Peritonitis, New England J. Med. **246**:52-54, 1952.

Synergism was most clearly demonstrable against micro-organisms which, like enterococci and many staphylococci, were peculiarly unresponsive to single drugs. In such cases the addition of another antibiotic in a concentration which alone appeared to have little or no effect, resulted often in a striking increase in rate of bactericidal action and the killing of all exposed micro-organisms in vitro. This definition is reiterated because others have employed the term synergism to describe results obtained with different methods and of different significance.[8] The synergistic effect of several drugs against a variety of micro-organisms in the test tube [4b] was paralleled by the ability of such drug pairs to enhance the cure rate of acute or subacute experimental infections in mice.[9] However, the most clear-cut illustrations of antibiotic synergism came from the successful treatment of patients with otherwise incurable bacterial endocarditis. Cases of enterococcal endocarditis cured with combinations of antimicrobial agents are now almost legion,[10] and there are at least scattered reports of endocarditis due to other drug-resistant organisms that responded to synergistic drug combinations.[11] For a host of other infections, chemotherapeutic synergism has been claimed, but because of the complexity of clinical evaluation and the lack of unambiguous data, there are few reports that may be accepted unequivocally. Brucella infection treated with drug combinations [12] perhaps comes closer than others to clear-cut synergism in the sense used here.

It may be stated in summary that both antagonism and synergism among antimicrobial drugs have been encountered in test-tube experiments, in infections of laboratory animals, and in specific human microbial infections. It is too early for a final assessment of the clinical importance of these phenomena, but it appears likely that they will have to be taken into serious consideration in antibiotic treatment in the future.

OBSERVATIONS ON THE MODE OF ACTION OF ANTIBIOTIC ANTAGONISM AND SYNERGISM

The precise mode of action is not known for a single antibiotic, in spite of years of intensive investigation. It seems futile, therefore, to approach the problem of combined antibiotic action from a theoretical side. Nevertheless, it may be of

8. Armstrong, C. W. J., and Larner, A. E.: The Effect of Combinations of Antibiotics on Pseudomonas Aeruginosa and on Proteus Vulgaris in Vitro and in Vivo, J. Lab. & Clin. Med. **37**:584-592, 1951. Bliss, E. A.; Warth, P. T., and Long, P. H.: Studies of Combinations of Antibiotics in Vitro and in Experimental Infections in Mice, Bull. Johns Hopkins Hosp. **90**:149-169, 1952.

9. Speck, R. S., and Jawetz, E.: Antibiotic Synergism and Antagonism in a Subacute Experimental Streptococcus Infection in Mice, Am. J. M. Sc., to be published.

10. Hunter.[3] Cates and others.[7a] Robbins, W. C., and Tompsett, R.: Treatment of Enterococcal Endocarditis and Bacteremia: Results of Combined Therapy with Penicillin and Streptomycin, Am. J. Med. **10**:278-299, 1951.

11. Volini, I. F., and Kadison, E. R.: Simultaneous Bacitracin and Penicillin Therapy in Subacute Bacterial Endocarditis, Am. Pract. & Digest Treat. **2**:13-14, 1951. Spies, H. W.; Dowling, H. F.; Lepper, M. H.; Wolfe, C. K., and Caldwell, R.: Aureomycin in the Treatment of Bacterial Endocarditis Together with a Study of the Synergistic Action of Aureomycin and Penicillin in One Case, A. M. A. Arch. Int. Med. **87**:66-78, 1951. Kirby, W. M. M.: Personal communication to the author. Jawetz, E.; Gunnison, J. B., and Speck, R. S.: Antibiotic Synergism and Antagonism, New England J. Med. **245**:966-968, 1951.

12. Herrell, W. E., and Barber, T. E.: New Method for Treatment of Brucellosis, J. A. M. A. **144**:519-524, 1950. Werner, C. A., and Knight, V.: The Suppressive Effect of Antimicrobial Drugs on Brucella Melitensis Infections in Mice, J. Immunol. **65**:509-514, 1950. McCullough, N. B., and Eisele, W.: Personal communication to the author.

interest to summarize certain observations made in the course of our studies and to see whether they may aid in the formulation of concepts and hypotheses on combined antimicrobial effects.

For the demonstration of antagonism in vitro, a bacteriostatic amount of the interfering agent must be added to an actively bactericidal quantity of the effective drug (Fig. 2). The interference effect has been attributed to the fact that "effective" drugs like penicillin or streptomycin act optimally on multiplying micro-organisms, and that drugs like aureomycin or chloramphenicol which are principally bacteriostatic consequently interfere with the "effective" agents.[13] Bacteriostasis per se, however, cannot be made responsible, for, if it is induced by minute amounts of the "effective" drugs themselves, there is no interference with subsequent larger doses of the same drugs acting on the now "static" population.[4f] Also there is no antagonism between bacteriostatic amounts of one member of a synergistic drug pair and any concentration of the other member. It seems, therefore, that antagonism must be based on a more specific interference by one drug with metabolic processes essential for optimal action of another drug.[4f] It is true that these metabolic activities must be commonly associated with growth and multiplication of micro-organisms, for in the absence of nutrient and energy sources antibiotic antagonism no longer occurs.[4e]

Definite limitations of time and dose relationship influence the occurrence of antibiotic antagonism. The interfering agent must act before, or simultaneously with, the effective one, not later. This limitation is most pronounced with sulfonamides, which must act for some hours prior to penicillin in order to antagonize it in vitro or in vivo.[5] Antagonism is greatest with concentrations of the interfering agents that are barely biologically active. The phenomenon is suppressed by a large excess of either of the participating drugs.[4b-f] Thus, the range of doses in which antagonism may occur is limited, and the likelihood of its observation in clinical practice is restricted. It should be noted that in the only instance in which antagonism has been unequivocally established in human disease (pneumococcal meningitis [6]) circumstances were ideally suited to its occurrence (i. e., combination of one very effective drug with a static agent, both present in critical concentration, but without any excess, at site of bacterial proliferation).

Antibiotic antagonism is not the result of chemical or physical interference with the action of drugs.[4c] Aureomycin acts as an interfering agent only when it is biologically active, not when it is inactivated by gentle heating or storage. The biologically active *levo*-form of chloramphenicol functions as an antagonist, but not the biologically inert *dextro*-form.[14] A hypothesis for a mode of action, adapted from Eagle,[15] may be presented schematically as follows: A given micro-organism utilizes a metabolic pathway $A \rightarrow B \rightarrow C \rightarrow D$. The "effective" drug can block it between C and D with accumulation of C, which is toxic and results in rapid death. The interfering agent blocking earlier steps in the pathway results in diminished synthesis of C and thus interferes with optimal action of the "effective" drug. If the interfering drug is present in sufficient concentration to block the pathway efficiently, then it becomes the rate-limiting event in the metabolic chain and makes the observation of antagonism impossible. An excess of the "effective" drug might

13. Hunter,[3] Jawetz, and others.[4c]

14. Gunnison, J. B.; Shevky, M. C., and Jawetz, E.: Unpublished data.

15. Eagle, H.: Further Observations on the Zone Phenomenon in the Bactericidal Action of Penicillin, J. Bact. **62**:663-668, 1951.

overcome antagonism by acting on more than one site of the metabolic pathway, as postulated by Eagle.[15] It is of interest that Browning and associates in 1922 [16] attributed interference among trypanocidal substances to "combination of both chemical substances with the same haptophore groups of the trypanosomes' protoplasm."

Positive summation of drug action (in excess of simple addition) may occur in a number of ways.[17] Thus, the two drugs acting simultaneously might affect different members of the microbial population, some of which are resistant to one agent, some to the other. Or one drug might prevent the rapid emergence of microbial forms resistant to the other drug; this is probably the reason for the increased effectiveness of the treatment of tuberculosis with combinations of strepto-

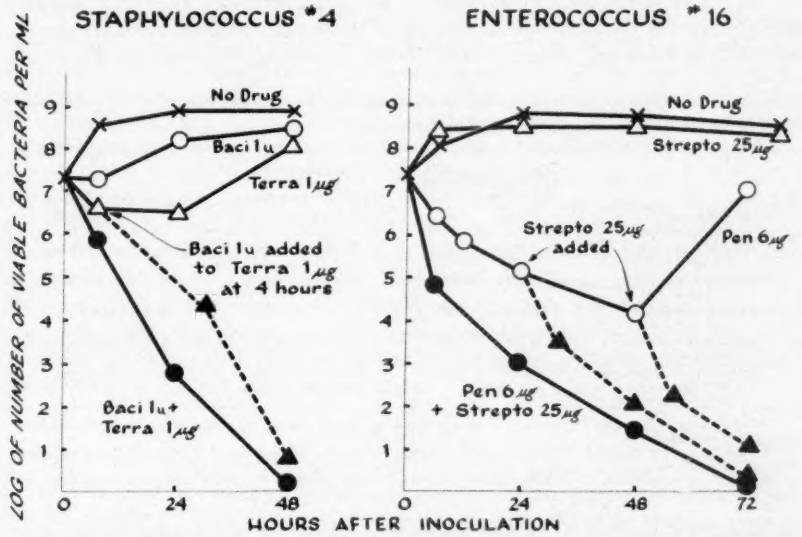

Fig. 3.—Immediate increase in rate of bactericidal action which results from addition of one member of a synergistic drug pair to the other. *Baci* stands for bacitracin; *Terra,* for terramycin; *Strepto,* for streptomycin, and *Pen,* for penicillin.

mycin and paraaminosalicylic acid or sulfones. In the antibiotic synergism discussed here, these mechanisms apparently are of no importance. Its outstanding characteristic is the immediate increase in rate of bactericidal action upon the addition of an apparently ineffective concentration of one agent to a somewhat active amount of the other (Fig. 3). This usually results in the rapid death of the entire exposed microbial population. There is no evidence to suggest that the two drugs of a

16. Browning, C. H., and Gulbransen, R.: An Interference Phenomenon in the Action of Chemotherapeutic Substances in Experimental Trypanosome Infections, J. Path. & Bact. **25**:395-398, 1922.

17. Miles, C. P.; Coleman, V. R.; Gunnison, J. B., and Jawetz, E.: Antibiotic Synergism Requires the Simultaneous Presence of Both Members of a Synergistic Drug Pair, Proc. Soc. Exper. Biol. & Med. **78**:738-741, 1951.

synergistic pair combine chemically to form a compound more effective than either drug alone. The possibility was investigated that one drug might so alter cellular surface or permeability as to improve the second agent's efficacy. It was postulated that in such circumstances synergism should occur if the micro-organisms were exposed to the members of a synergistic pair in rapid sequence, rather than simultaneously. Suitable experiments, however, failed to support this idea. Antibiotic synergism required the simultaneous presence of both drugs.[17]

With a synergistic pair of drugs the effect is demonstrable over a wide range of doses. Only one member of the pair need exhibit biological activity alone; the other may be ineffective in the concentration entering into synergism, though having some influence on the micro-organism in a hundredfold or thousandfold larger amount.[18]

On survey of the available evidence, it seems that antibiotic synergism may be best explained by the simultaneous blocking of interacting metabolic pathways essential for growth. If one pathway were blocked by a drug, the organism might be

TABLE 2.—*Examples of Antagonism and Synergism Resulting from Interaction of Antibiotics of Groups I and II* *

	Antibiotics, γ/Ml.† Inhibiting for 24 Hr. When Acting Alone		Killing 99.99%‡ in 24-48 Hr. When Acting Alone		Combined Action
Penicillin-sensitive Streptococcus	P 0.003	C 3.0	P 0.006	C 20	P + C antagonism
Penicillin-resistant Proteus	P 20.0	C 10.0	P 50.0	C 100.0	P + C synergism
Bacitracin-sensitive Streptococcus	B 0.001	T 0.5	B 0.01	T 10.0	B + T antagonism
Bacitracin-resistant Staphylococcus	B 5.0	T 1.2	B 10.0	T 10.0	B + T synergism
Streptomycin-sensitive Klebsiella	S 1.0	T 0.5	S 2.0	T 20.0	S + T antagonism
Streptomycin-resistant Staphylococcus	S 25.0	T 20.0	S 50.0	T 50	S + T synergism

* Data from Jawetz and Gunnison.[18] P means penicillin; B, bacitracin; S, streptomycin; C, chloramphenicol, and T, terramycin.

† Inhibiting concentration: Smallest amount of drug preventing visible growth in 24 hours, from an inoculum of ca. 10^6 cells.

‡ Killing concentration: Smallest amount of drug which reduced to viable bacterial population by 99.99% in 24 to 48 hours.

temporarily restrained in growth and multiplication but would soon utilize other pathways with greater efficiency and thus bypass the drug block. If however, two or more synthetic pathways were blocked, the organism might die. This supposed mode of action must remain entirely speculative until a direct biochemical approach to the problem becomes possible.

A SCHEME OF COMBINED ANTIBIOTIC ACTION

The available basic information about combined antibiotic action, summarized above, should make it possible to approach the subject rationally. Is it then possible for therapeutic purposes to denote certain drug combination as "good" and others as "bad"? It must be stated with greatest emphasis that fixed "synergistic" or "antagonistic" drug pairs do not exist. A given combination may be synergistic against one micro-organism, may be antagonistic against a second, and may be

18. (*a*) Jawetz and others.[4b] (*b*) Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism: A Scheme of Combined Antibiotic Action, Antibiotics & Chemother., to be published.

indifferent when acting on a third (Table 2). It is the behavior of the specific micro-organism when treated with the component members of the pair that determines the combined drug effect.[19] Even strains of a given microbial species or variants derived from the same strain do not behave uniformly with respect to a certain drug pair. This makes it clear that, for the time being, synergistic drug combinations against a specific organism can be determined only by detailed and cumbersome laboratory study. To facilitate and simplify this approach, we have found it useful to arrange antibiotic agents into a scheme which permits certain predictions of combined drug action. The details and limitations of the scheme have been presented elsewhere,[18b] and only the essential points are outlined here.

Antibiotics may be arranged in two groups:

I. Penicillin, streptomycin, bacitracin, neomycin

II. Aureomycin, chloramphenicol, terramycin

Members of Group I are frequently synergistic with each other, occasionally indifferent, never antagonistic. Members of Group II are neither synergistic with nor antagonistic to each other, but simple additive effects are often observed, effects which are presumably also obtainable by an increase in the dose of a single drug. Sulfonamides may fit into Group II. When a member of Group II is added to a drug of Group I, their combined effect apparently depends on the susceptibility of the micro-organism to the Group I drug. With a micro-organism susceptible to a Group I drug, antagonism may result; with a micro-organism resistant to a Group I drug, synergism may result. This scheme is entirely hypothetical but is, at present, in agreement with conclusive experimental and clinical data.[18b] It is presented as a guide of temporary usefulness but should be modified or abandoned when new information proves it to be inadequate. We have found the scheme helpful in the planning of experiments and in the selection of drug combinations for treatment of specific infections of patients.

CONCLUSIONS

A synopsis is presented of experimental information pertaining to the combined action of antimicrobial agents, together with some speculations concerning the mode of action involved. Only an encouraging beginning has been made in the exploration of this field, which promises to be of both fundamental and practical importance, and it may be hoped that future work in this area will be rewarding.

19. Jawetz and others.[4f] Gunnison and others.[14]

ERYTHEMA MULTIFORME EXUDATIVUM

Study of Fifteen Cases

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ERYTHEMA multiforme exudativum is by no means a rare disease. Unfortunately, this malady has been reported under a variety of labels and eponyms, so that up to very recently the picture was almost a mass of utter confusion. A timely and recent editorial in *The Journal of the American Medical Association* [1] concerning this condition is worthy of careful perusal.

In 1860, Hebra [2] described a new clinical picture under the name erythema multiforme exudativum. In 1862, Alibert and Bazin [3] described lesions in the mouth associated with constitutional symptoms and distinguished the herpetic lesion of the iris. In 1922, Stevens and Johnson,[4] in describing what they called a "new eruptive fever," stressed as their criteria for diagnosis a generalized maculopapular eruption associated with ulceromembranous stomatitis, purulent conjunctivitis, and fever. In 1937, Klauder [5] popularized in this country a new symptom complex known in the French literature as *ectodermosis erosiva pluriorificialis*. This was described as a disease of acute onset with chills, fever, vesicular and bullous skin lesions, vesiculation of the buccal mucosa, mild conjunctivitis, and genital ulcerations with urethritis. Behcet,[6] in 1940, reported his observation on a so-called triple symptom complex (known since as Behcet's disease), consisting of aphthous ulcers in the mouth, aphthous ulcers on the genitalia, episcleritis, and erosion on the cornea, associated with erythema-multiforme-like skin lesions, furuncles, and erythema nodosum. However, a careful study of the cases presented reveals the similarity among these syndromes and shows that these entities are but variants of erythema multiforme exudativum. An elaborate classification into distinct entities serves no

From the Medical Service of Harlem Hospital, Dr. Alexander Altschul, Director of Medicine.

1. Erythema Multiforme Exudativum, editorial, J. A. M. A. **146**:1424 (Aug. 11) 1951.

2. von Hebra, F.: On Diseases of the Skin, Including the Exanthemata, London, The New Sydenham Society, Vol. 1, 1866.

3. Alibert and Bazin, cited in editorial.[1]

4. Stevens, A. M., and Johnson, C. F.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:256 (Dec.) 1922.

5. Klauder, J. V.: Ectodermosis Erosive Pluriorificialis: Its Resemblance to Human Form of Foot and Mouth Disease, and Its Relation to Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

6. Behcet, H.: Some Observations on the Clinical Picture of the So-Called Triple Symptom Complex, Dermatologica **81**:73 (Feb.) 1940.

useful purpose and merely tends to confuse rather than clarify the subject. Later reports by others stressed the upper respiratory and pulmonary complications observed. Finland [7] found pneumonia in his patients resembling the severe and diffuse type of primary atypical pneumonia of unknown causation in every respect, clinically, roentgenologically, and pathologically.

Erythema multiforme exudativum is a disease with protean manifestations and lies within the domain of the internist and general practitioner. It is they who in the past have failed to recognize this entity, and thus have referred their patients to eye and skin consultants, depending upon the predominant lesions presented. Therefore, much of the knowledge concerning this disease has come from the dermatologist and ophthalmologist, as well as the pediatrician. It is noteworthy that the latest edition of Cecil's [8] "Textbook of Medicine," published in 1951, devotes only three paragraphs to this malady, with practically no mention of diagnostic criteria for its recognition. However, the management of this disease should lie in the hands of the medical practitioner, and consultation should be employed as in every other medical condition.

There is considerable speculation about the causation of erythema multiforme exudativum, but to date a specific etiological agent has not been discovered. Results of laboratory and bacteriologic studies have been negative and confusing. Virus causation was suggested by the work of Anderson [9] in 1949. He reproduced keratoconjunctivitis in rabbits' eyes with vesicular fluid obtained from a patient who had erythema multiforme exudativum and demonstrated cytoplasmic inclusion bodies. However, this has been unconfirmed by other workers. Finland [7] demonstrated psittacosis antibodies in two cases and noted lesions of the lungs resembling viral pneumonia in several cases. Klauder [5] tried to grow the virus of foot and mouth disease from his cases but did not succeed.

Other authors have invoked allergy as an etiological factor. However, except for the evidence presented by Thomas [10] and Straus,[11] the results were scanty. Thomas [10] described a woman who had four relapses, each following a small dose of sulfonamide, while Straus [11] reproduced an attack of erythema multiforme exudativum by repeated administration of sulfonamide. One of us (B. W. B.),[12] while in the United States Army, reported observations on mass prophylactic sulfadiazine medication given to 20,000 soldiers daily for five weeks. There were 63 who reacted adversely to the drug; of these, 52 had skin reactions. Of the 52 with skin rash, 30

7. Finland, M.; Jolliffe, L. S., and Parker, F., Jr.: Pneumonia and Erythema Multiforme Exudativum, Am. J. Med. **4**:473 (April) 1948.

8. Textbook of Medicine, Ed. 8, edited by R. L. Cecil and R. F. Loeb, Philadelphia, W. B. Saunders Company, 1951, p. 480.

9. Anderson, J. A.; Bolin, V.; Sutow, W. W., and Kitto, W.: Virus as Possible Etiologic Agent of Erythema Multiforme Exudativum, Bullous Type: Report of Case, Arch. Dermat. & Syph. **59**:25 (March) 1949.

10. Thomas, B. A.: So-Called Stevens-Johnson Syndrome, Brit. M. J. **1**:1393 (June 17) 1950.

11. Straus, D. A.: Generalized Bullous Eruption Following Testing for Sulfonamide Hypersensitivity, New England J. Med. **239**:956 (Dec. 16) 1948.

12. Billow, B. W., and Albin, M. S.: Observations on Mass Chemo-Prophylaxis with Sulfadiazine, Ann. Int. Med. **24**:863 (May) 1946.

had fever as well. The skin reactions cleared within 48 hours. Not one case was seen which resembled erythema multiforme exudativum in any form. Yet other authors [13] described cases of erythema multiforme exudativum occurring during the administration of sulfadiazine, with fatal termination. In addition, phenobarbital and phenolphthalein have been reported to cause a condition resembling erythema multiforme exudativum. One of our patients (Case 7), described more fully in the table, presented all the cardinal signs of erythema multiforme exudativum after swallowing a dose of "666 Cold Preparation" (a preparation of antipyrine, citric acid, magnesium sulfate, and ammonium chloride), with recurrence two years later. Another patient (Case 1) also gave a history of taking pills before onset of disease, but here the history was equivocal. Unfortunately, we can only speculate about the causation but can offer no elucidation as yet.

Erythema multiforme exudativum is an acute febrile and debilitating disease. It lasts from two to four weeks. This disease is not as uncommon as it is reported to be, and if the condition is looked for by the clinician many more cases will be found. It has been confused with many other diseases, such as pemphigus, chickenpox, impetigo, rheumatic fever, rash due to drugs, erythema nodosum, and Henoch-Schönlein syndrome. However, if one bears in mind the cardinal signs and symptoms of this disease, the diagnosis may be made with fair accuracy. One is struck by the toxicity these patients present. They really look sick. They appear dehydrated and somnolent. An analysis of the literature and of our cases, which we will further discuss under Comment, shows the following criteria necessary for the diagnosis of this entity. They are multiforme-like skin and mucous-membrane lesions involving lips, buccal membrane, and genitalia; the presence of eye lesions, and toxicity. The disease is commonest below the age of 30 [14]; however, it may occur in persons of all age groups. Most of our patients were females, although the literature shows a male preponderance.[14] There are generally associated fever, malaise, sore throat, and, at times, joint pains, as well as pulmonary complications. Recurrences have been noted in the literature, as well as fatalities. There have been two recurrences in one of our patients and three in another. We had one case with fatal termination.

Treatment of erythema multiforme exudativum has been chiefly symptomatic and unsatisfactory. Many authors claim improvement with sulfonamides and penicillin,[15] although most found little or no effect. Our patients' response to penicillin was equivocal. Church [16] and Lynas [17] found aureomycin caused dramatic improvement. We have used this drug but are not convinced of its specificity. Fishman [18] presented a case of severe erythema multiforme exudativum bullosum treated topi-

13. Greenberg, S. I., and Messer, A. L.: Fatal Bullous Dermatitis Following Administration of Sulfadiazine, J. A. M. A. **122**:944 (July 31) 1943. Dardinski, V. J.: Erythema Multiforme Bullosum Following Use of Sulfadiazine, Am. J. Clin. Path. **15**:28 (Jan.) 1945.

14. Ashby, D. W., and Lazar, T.: Erythema Multiforme Exudativum Major (Stevens-Johnson Syndrome), Lancet **1**:1091 (May 19) 1951.

15. Wright, D. D.; Gold, E. M., and Jennings, G.: Stevens-Johnson Syndrome: Report of 9 Patients Treated with Sulfonamides or Penicillin, Arch. Int. Med. **79**:510 (May) 1947.

16. Church, W. E.: Erythema Exudativum Multiforme and Pneumonitis Treated with Aureomycin, Lancet **1**:281 (Feb. 11) 1950.

17. Lynas, M. A.: Aureomycin in Stevens-Johnson Syndrome, Lancet **1**:373 (Feb. 25) 1950.

18. Fishman, H. C.: Topical Use of Cortisone in Erythema Multiforme Bullosum, California Med. **74**:5 (May) 1951.

cally with cortisone. He found that at the end of three days 90% of the lesions had involuted completely, leaving only slight erythema. There is no doubt in our minds that antibiotics should be used for the suppression of the secondary infection which is always found in this disease, but we question strongly their specificity. It is important that supportive measures, such as administration of adequate fluids and electrolyte studies, be carried out.

The table presents the essential characteristic findings in our cases.

COMMENT

Erythema multiforme exudativum is by no means as uncommon as it is purported to be. We have seen six cases in the past few months in an "acute, miscellaneous medical service" at Harlem Hospital. An awareness of the disease and its signs will result in its recognition.

In the cases presented, certain facts emerge and are worthy of comment. In order to recognize this entity and prevent errors in diagnosis, it may not be amiss to repeat the findings of Fletcher and Harris.[19] They reported on 16 patients with erythema multiforme exudativum bullosum, of whom only 1 was sent to the Willard Park Hospital, New York, with a correct diagnosis. Therefore, we should like to stress and emphasize the major or cardinal diagnostic criteria, as well as the less frequent but also important associated findings, which establish this disease as an entity.

Specific and Most Frequent Diagnostic Signs in Erythema Multiforme Exudativum.—These are

I. Toxic Appearance of Patients: All our patients and most of those described in the literature looked acutely ill. They appeared to be in distress and dehydrated. One is struck, upon looking at the patient, by the severity of the illness.

II. Eye Lesions: These were present in 10 of our 15 patients. They were characterized by bilateral conjunctivitis with exudate. Some patients had blepharitis and edema of the lids. Other authors reported keratitis or panophthalmitis, often severe enough to cause blindness. Fortunately, whether because of antibiotic therapy or not, the lesions in our cases were mild and left no residue.

III. Mucous Membrane Lesions:

A. Lips: These were present in 13 of our 15 patients. They were characterized by redness, edema, fissuring, and hemorrhagic ulcerations, with residual crusting.

B. Genitalia: Penile or vulvovaginal lesions were present in 14 of our 15 patients and were characterized by swelling, redness, and ulcerations, at times associated with nonspecific urethritis.

C. Buccal Cavity: These were present in 14 of our 15 patients and were characterized by pseudomembranes and ulcerations of vesiculations often involving the tongue, pharynx, and palate.

IV. Skin Rash: Skin rash was present in all our patients. It was most commonly of a maculopapular, vesicobullous, and hemorrhagic type. Its distribution was generalized except for the scalp, which was free of rash in 14 of our 15 patients.

19. Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra)—Bullous Type: Cases Seen in a Contagious Disease Hospital, J. Pediat. **27**:465 (Nov.) 1945.

Case Histories

Case No.	Age, Yr.	Sex	Prodromal Symptoms	Appearance	Skin Lesions	Lips
1	25	F	Head cold and cough; went to drugstore for remedy; took pills (content unknown) and became ill soon thereafter	Acutely ill and toxic	Vesicular, hemorrhagic, bullous, maculopapular; generalized, including scalp	Swelling with ulceration and crust of blood
2	18	F	Sore throat; fever; chill	Acutely ill and toxic	Vesicular, hemorrhagic, bullous, maculopapular; generalized, except for scalp	Edematous, cracked, with crusts of blood
3	21	F	Sore throat; malaise; chill and fever	Acutely ill and toxic	Papular, bullous, and hemorrhagic ulcerations	Ulcerated and bleeding
4	20	F	Malaise; fever; diarrhea	Acutely ill and toxic	Papular ulcerations and hemorrhages; generalized, except for scalp	Not involved
5	40	M	Malaise; cough; fever	Acutely ill, disoriented, toxic	Bullae, ulcerations, hemorrhagic, rash; generalized, except for scalp	Ulcerated, cracked, with blood
6	52	M	Malaise	Acutely ill and toxic	Bullae; denuded ulcerations over thorax; extremities slightly involved in patches; scalp not involved	Swollen, ulcerations
7	57	M	Admitted in Dec., 1951, after taking "606" for cold; previous attack in 1949 following "606"; no recurrences between	Acutely ill and toxic	Papular ulcerative, hemorrhagic; generalized, except for scalp; areas of hyperpigmentation over face	Swollen, red, with ulcerations and bleeding
8	3	M	Lethargy; irritability	Acutely ill and toxic	Macular, papular, bullous and hemorrhagic rash; generalized, except for scalp	Edematous, ulcerated, with crusts of blood
9	10 mo.	M	Restlessness; fever	Acutely ill and toxic	Papular, vesicular, bullous rash; generalized, except for scalp	Swollen, ulcerated
10	41	M	Sore throat; difficulty in swallowing; fever	Toxic and lethargic	Papular, vesicular, bullous; generalized, except for scalp	Not involved
11	28	F	Sore throat; malaise; fever; this is 3d attack within 6 yr.	Acutely ill	Macular, papular, hemorrhagic; generalized, except for scalp	Hemorrhagic; crusting
12	20	M	Malaise; sore throat; fever; difficulty in swallowing	Acutely ill, in distress, and dehydrated	Macular, papular, ulcerations; hemorrhagic; generalized, except for scalp	Swollen, red, bleeding
13	35	F	Sore mouth; malaise; sore throat, inability to swallow	Acutely ill and toxic	Macular, papular, hemorrhagic; generalized, except for scalp	Dry with crusted blood and ulceration
14	2	F	Malaise; fever	Acutely ill and toxic	Hyperemia, vesicles, bullae, hemorrhagic, rash; generalized, except for scalp	Swollen with crusts of blood
15	10	F	Headache; fever; sore throat	Acutely ill and and toxic; dehydrated	Macular, papular rash; generalized, except for scalp	Swollen, vesicles, cracked

Less Frequent Signs in Erythema Multiforme Exudativum.—These are

I. Pneumonitis: The association of pulmonary pathology with erythema multiforme exudativum was stressed in this country by the Commission On Acute Respiratory Diseases.[20] Canadian authors,[21] in reporting 17 cases of erythema

20. Commission on Acute Respiratory Diseases: Association of Pneumonia with Erythema Multiforme Exudativum, Arch. Int. Med. **78**:687 (Dec.) 1946.

21. Stanyon, J. H., and Warner, W. P.: Mucosal Respiratory Syndrome, Canad. M. A. J. **53**:427 (Nov.) 1945.

Case Histories

Buccal Membranes	Eyes	Genitalia	Treatment	Hospital Course
Stomatitis; vesicles over palate and sides of tongue and pharynx	Conjunctivitis, blepharitis	Not involved	Penicillin	Stormy for 4 wk.; not influenced by antibiotics
Hemorrhagic ulcerations of gums; pseudomembrane over tonsils, with hyperemia	Conjunctival hemorrhages, keratitis, edema of lids	Vaginal discharge with ulcerations and edema of labia	Penicillin	Patient did not respond in spite of symptomatic antibiotic treatment and died
Mucous patches in mouth; ulcerations at tip and lateral surface of tongue; pharynx infected	Bilateral conjunctivitis	Vaginal discharge with ulcerations over mucous membrane	Aureomycin started 7th day	Patient treated symptomatically for first 7 days without response; noted improvement after administration of aureomycin
Stomatitis; tonsils hyperemic, covered with thick exudate	Bilateral conjunctivitis with exudate	External swelling of labia	Symptomatic	Cured after 4 wk.
Vesicles over palate; pharynx red; tonsils infected and covered with white membrane	Conjunctivitis with purulent secretions	Ulceration, tip of penis	Aureomycin	Patient had clinical and x-ray evidence of left lower lobe pneumonia; had stormy course in spite of aureomycin therapy
Not involved	Bilateral conjunctivitis	Denuded ulcerations over penis	Aureomycin started 3d day by resident	Improvement noted before aureomycin therapy; cleared within 8 days
Pharynx infected; vesicles over palate; ulcerations of tongue	Bilateral conjunctivitis	Scrotum denuded with penile ulcerations	Aureomycin given immediately	Stormy course with no improvement for first few days; cleared in 4 wk.
White mucous patches over tonsils and gums; ulceration of tongue	Conjunctival infection with purulent discharge; lids swollen	Penis swollen, red	Penicillin	Patient had clinical and x-ray evidence of left lower lobe pneumonia; cleared in few wk.
Gums and palate covered with vesicles and ulcerations; tonsils hyperemic	Not involved	Penis swollen; prepuce excoriated; scrotum edematous with ulceration	Penicillin	Improved in 14 days
Pseudomembranes over tonsils; ulcerations of tongue; stomatitis	Not involved	Penis edematous; scrotum edematous with vesiculation and ulcerations	Penicillin	Stormy course; cured in 4 wk.
Mucous patches over palate, with ulcerations of gum and tongue	Not involved	Vaginal discharge	Penicillin	Cured in 3 wk.
Vesicles over palate and gums; ulcerations of tongue; pharynx red	Not involved	Penile ulcerations, with discharge	Penicillin	Cured in 4 wk.
Mucous patches over pharynx and tonsils; stomatitis	Not involved	Vulva swollen, red, with ulcerations	Penicillin	Cured in 4 wk.
Stomatitis with ulceration; tonsils inflamed, covered with patchy exudate	Conjunctival infection with purulent discharge	Vulva inflamed and swollen, with vaginal discharge	Symptomatic	Cured in 10 days
Aphthous ulcers in mouth and palate; pharynx red	Conjunctival infection; lids swollen and red	Excoriation of labia with vaginal discharge	Penicillin	Cured in 14 days

multiforme exudativum, found 14 of them associated with pneumonitis. We had two proved cases of pneumonia in our series.

II. Sore Throat: Sore throat occurred with or without difficulty in swallowing.

III. Malaise

IV. Joint Pains

V. Erythema Nodosum

We do not intend to imply that all the major signs described above must be present for the diagnosis of erythema multiforme exudativum. We do wish to emphasize, however, that the lesions most frequently found are characteristic of this disease. Our case histories show that all our patients had a minimum of five of the six cardinal signs which we consider diagnostic criteria. In addition, all our patients had one or two of the less frequent symptoms. Thus, in our opinion, the presence of a minimum of any four of the symptoms enumerated under "specific and most frequent diagnostic signs" should direct one's attention to erythema multiforme exudativum.

Fig. 1 (Case 1).—Typical lesion of lips in erythema multiforme exudativum. Note crust of blood.

It is apparent from our case histories that 13 patients gave no history of or any association with drug intake, while Cases 1 and 7 involved the use of medication prior to the onset of illness. The first patient (Case 1) admitted having taken pills for a cold, the contents of which were unknown. She became ill soon after. The other patient (Case 7) gave a history of a previous attack in 1949 after first swallowing a dose of liquid "666." He was hospitalized at that time and presented symptoms similar to those of the recent attack. He was admonished not to take the drug again. He abstained until a few weeks ago, when he again took the same

medicament. He again became ill and was admitted to the hospital, where examination revealed the signs described in his case history. Thus, two patients obviously manifested idiosyncrasy or hypersensitivity to drugs, presented all the diagnostic features of erythema multiforme exudativum, and were indistinguishable clinically from our other 13 patients in whom the cause of the disease must be attributed to an infectious agent of unknown origin. Laboratory studies in our cases, including com-

Fig. 2 (Case 7).—Involvement of lips and upper extremities in erythema multiforme exudativum.

plete blood cell count, blood cultures, epithelial scrapings from conjunctiva, and vaginal and penile smears, were all noncontributory. Blood sugar, urea, protein, and liver-function studies were nonrevealing.

Our treatment of erythema multiforme exudativum has been symptomatic. We have used penicillin in eight patients and have administered aureomycin to four. No dogmatic assertions can be made regarding the efficacy and specificity of either drug. The most we can say is that we found them useful in controlling the spread

of secondary infections. Goldfarb,[22] listing 21 cases, stated that all patients treated with sulfonamides retained normal sight, whereas, of those not so treated, seven became partially blind. We also feel that the use of antibiotics resulted in no serious residual effects in our patients, but we cannot claim any dramatic cures with them.

Fig. 3 (Case 7).—Penile involvement in erythema multiforme exudativum.

Now, with the advent of cortisone and corticotropin (ACTH) it will be interesting to observe their influence, if any, upon this disease. We shall use them henceforth for all our new patients.

22. Goldfarb, A. A.: Case of Stevens-Johnson Disease: Erythema Multiforme Bullosa Treated with Penicillin, J. Pediat. **28**:579 (May) 1946.

CONCLUSIONS

We recommend that the term erythema multiforme exudativum be used to signify a recognized entity rather than the eponyms Stevens-Johnson syndrome, Behcet's disease, Hebra's disease, etc., heretofore used. These terms only confuse and delay the recognition of this entity.

Case histories of 15 patients with erythema multiforme exudativum are presented.

Emphasis is laid on the diagnostic features of this disease.

The causation of erythema multiforme exudativum is not elucidated. Two of our patients became ill as the result of a noxious agent (hypersensitivity or allergy to a drug), while the causation in the others was of probable infectious origin. Laboratory studies have been fruitless.

No specific treatment has been found. We used aureomycin and penicillin without any dramatic results.

PAROXYSMAL VENTRICULAR FIBRILLATION PRODUCING ADAMS-STOKES SYNDROME

Report of Case with Review of Literature

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INCREASING interest in the relative importance of paroxysmal ventricular fibrillation, as opposed to ventricular standstill, as the cause of Adams-Stokes seizures has encouraged us to report another case and to review the present concepts concerning various features of the condition, including etiology, prognosis, prevention, and treatment. Interest in this problem is justified particularly since efforts toward prevention of attacks and rational treatment of Adams-Stokes seizures depend upon the identification of the basic underlying mechanism, namely, paroxysmal rapid heart action (including ventricular tachycardia, prefibrillary ventricular tachycardia, and ventricular fibrillation) or ventricular standstill. Our interest in the problem has been stimulated by a case which we have had the opportunity to observe and study.

REPORT OF CASE

Present History.—A physician, 64 years of age, was admitted to the hospital March 20, 1947, because of an attack of syncope four days before entry. Upon falling in his bathroom, he had struck his head and later the same day had a convulsion lasting five minutes with complete absence of breathing, so that artificial respiration was administered. The patient had no other complaint except that for five days he had noted symptoms of "influenza," characterized by malaise, nasal discharge, cough, and elevation of temperature to 101 F.

Past History.—Four months previously, in November, 1946, he had been hospitalized because of complete heart block associated with anterior myocardial infarction. One month prior to this previous admission, he had experienced an attack of unconsciousness lasting 15 minutes without apparent cause. The patient had noted no bradycardia, and there was no history of previous attacks. Angina pectoris had been noted on several occasions over a period of two years, but, in spite of moderate activity, there had been no symptoms for several months prior to admission. No history was obtained of previous myocardial infarction. An electrocardiogram, made in 1934 when the patient had symptoms of recurrent spontaneous pneumothorax, suggested only right axis deviation. He was known to have had mild diabetes since 1937, at which time fasting blood sugar was 170 mg. per 100 cc. The diabetes was controlled by diet without insulin. After his discharge from the hospital in December, 1946, he had shown steady improvement and had returned to part-time work in his office.

Results of Physical Examination.—The physical examination on admission to the hospital revealed a thin man in good general condition, with ecchymosis about the right cheek and forehead. The chest examination revealed no abnormality; the pulse rate was 40 per minute,

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with regular rhythm; the blood pressure was 145 mm. Hg systolic and 50 mm. Hg diastolic. Roentgenologic changes suggested pneumonitis in the right upper lobe, with indication of cardiac enlargement.

Laboratory Data.—The laboratory data were as follows: A complete blood cell count was normal; the sedimentation rate was 24 mm. in one hour (Cutler); the fasting blood sugar was

TABLE 1.—*Relationship Between Electrocardiographic Findings, Medicaments Administered, and Incidence of Adams-Stokes Attacks**

Date Oct., 1946	ECG Diagnosis*	Quinidine, Grains	Epineph-rine	Ephedrine, Grains, 3 Times a Day	Atropine, Grains, Every 4 Hr. I. M.	Penicillin, Units, Every 3 Hr. I. M.	Ammonium Chloride, Grains, Every 4 Hr.	Adams-Stokes Attacks Initial attack
Admitted 11/25/46	CHB; RBBB; anterior infarct	None	None	None	1/150	None	None	None
11/26/46	CHB; RBBB; anterior infarct	None	None	None	1/150	None	None	None
11/27/46	None	None	None	None	1/150	None	None	None
11/28/46	None	None	None	None	1/150	None	None	None
11/29/46	None	None	None	None	None	None	None	None
11/30/46	None	None	None	None	None	None	None	Dizzy
12/ 1/46	None	None	None	None	None	None	None	None
12/ 2/46	CHB; RBBB; T waves normal	None	None	None	None	None	None	None
12/ 3/46	None	None	None	None	None	None	None	None
12/ 4/46	None	None	None	1/16	None	None	None	None
12/ 5/46	None	None	None	1/16	None	None	None	None
12/ 6/46	None	None	None	1/12	None	None	None	None
12/ 7/46	None	None	None	1/12	None	None	None	None
12/ 8/46 Discharged	None	None	None	1/12	None	None	None	None
12/20/46 to 1/3/47	CHB; RBBB	None	None	None	None	None	None	None
3/16/47	None	None	None	None	None	None	None	1
Readmitted 3/20/47	CHB; LBBB; anterior infarct	None	None	None	None	50,000	None	None
3/21/47	CHB; LBBB; anterior infarct	None	None	3/8	None	50,000	15	None
3/22/47	None	None	None	3/8	None	50,000	15	None
3/23/47	None	None	None	3/8	None	50,000	15	None
3/24/47	CHB; RBBB; anterior infarct	3 t. i. d.; 2 doses (6 gr.)	None	3/8	1/150	None	15	None
3/25/47	CHB; RBBB; anterior infarct	3 t. i. d.; 3 doses (9 gr.)	None	3/8	1/150	None	None	Faint feeling, 2
3/26/47	CHB; RBBB	3 t. i. d.; 3 doses (9 gr.)	57 m. (1:1,000) I. M.	3/8	1/150	None	None	5
3/27/47	CHB; LBBB	20 i. v. 18 p. o.	44 m. I. M.	3/8	None	None	None	23
3/28/47	CHB; RBBB	6¼ i. v. 12 p. o.	1 cc. in heart	None None	None None	None None	None None	6 Death (4:15 a. m.)

* CHB is complete heart block; RBBB, right bundle branch block; LBBB, left bundle branch block; t. i. d. three times a day; i. v., intravenously; p. o., orally; m., minim, and I. m., intramuscularly.

148 mg. and nonprotein nitrogen 53 mg. per 100 cc. Urinalysis revealed a 3+ reaction for albumin with 4+ reaction for blood and pus. The electrocardiogram on admission suggested complete heart block with left bundle branch block and probable anterior myocardial infarction.

Clinical Diagnoses.—The tentative diagnoses on admission included arteriosclerotic heart disease with complete heart block, Adams-Stokes seizures (presumed, in retrospect probably erroneously, to be due to ventricular standstill), probable myocardial infarction, and atypical pneumonia or pulmonary infarct.

Clinical Course and Treatment.—The therapeutic program is outlined in Table 1.

Serial electrocardiograms were interpreted as indicating anterior myocardial infarction, so that on the fifth day the patient was given, prophylactically, quinidine sulfate, 0.2 gm. (3 grains) three times a day. On the sixth day the quinidine administration was temporarily discontinued, but, since he was found to have frequent premature ventricular contractions, producing a bigeminal rhythm, the quinidine therapy was begun again on the seventh day. After the administration of quinidine, there appeared frequent attacks of syncope associated with convulsions. Since the electrocardiogram made during one of the attacks suggested the presence of ventricular fibrillation, it was decided, after discussion and consultation, that quinidine therapy should be intensified. Subsequently the seizures, lasting three to five minutes with marked cyanosis and apnea, became more frequent. Electrocardiograms indicated paroxysms of prefibrillary ventricular tachycardia ("ventricular flutter") and ventricular fibrillation.

Because of the increasing frequency of the attacks, it was decided that quinidine should be given intravenously. This was done in dosages of 1 gm. (15 grains) diluted in 300 cc. of distilled water, given intravenously very slowly with constant medical attention and electrocardiographic observation, a direct-writing unit being employed. The ventricular fibrillation appeared to subside, but recurred within 30 minutes. An additional dose of 0.33 gm. (5 grains) of quinidine sulfate was given intravenously, with apparent temporary disappearance of prolonged paroxysms of ventricular fibrillation. It then was thought advisable, because of the recognized hazards of quinidine administered intravenously, to try increasing the oral dosage to 0.33 gm. (5 grains) every two hours for four doses and 0.2 gm. (3 grains) every two hours during the night. Later, in desperation and in view of the apparent hopeless situation, an additional 0.4 gm. (6 grains) of quinidine sulfate was given intravenously. However, the seizures recurred, so that the patient died in an attack of ventricular fibrillation, an electrocardiographic tracing being obtained during the terminal episode.

Autopsy Observations.—Postmortem examination revealed advanced sclerosis of the coronary arteries with calcification markedly narrowing the lumen. Many of the smaller branches, particularly of the anterior coronary artery, were occluded. There was severe arteriosclerosis with calcification around the bases of the aortic valve cusps, the process extending around the coronary ostia so as to narrow the openings. The weight of the heart was 326 gm., and the valves were grossly normal. Microscopic study revealed fibrous myocarditis with fatty infiltration. No recent fresh myocardial infarct was found. There was fibrosis of the lungs, involving particularly the right apex, but no recent pulmonary infarct was demonstrated.

COMMENT

Table 1 outlines the patient's course over the entire period of observation, particularly as related to therapy. A more detailed account is given in Table 2, showing the incidence of the Adams-Stokes seizures in relation to medications. Although seizures were noted on two widely spaced occasions prior to the administration of quinidine, none was observed during the period of hospitalization until after quinidine, 0.2 gm. (3 grains) three times a day, totaling 0.6 gm. (9 grains), was given. The frequency of the attacks increased with the continued administration of quinidine orally. The incidence seemed to be diminished while quinidine was being given intravenously, possibly because of the depressant effect on the heart muscle. However, the patient died in ventricular fibrillation after intensive quinidine administration, both orally and intravenously. In retrospect, it is felt that quinidine definitely aggravated the tendency toward the development of Adams-Stokes seizures.

During the first admission to the hospital in November and December, 1946, the cause of the previous Adams-Stokes attack, since no electrocardiogram during the seizure had been made, was thought to be ventricular standstill. For this reason, epinephrine was to be given in case of an attack. However, since none occurred, the drug was not administered. Ephedrine sulfate was given during the latter part of the hospital stay. At that time there was definite electrocardiographic evidence of

TABLE 2.—*Incidence of Adams-Stokes Attacks with Relationship to Medications*

		12 Mid.	1	2	3	4	5	6 a. m. 6	7	8	9	10	11	Noon 12	13	14	15	16	17	6 p. m. 18	19	20	21	22	23	24 Mid.
3/24/47	Ephedrine, grains	..	..	..	..	..	..	..	..	¾*	..	..	..	..	..	..	..	¾*	..	..	..	..	..	¾*	..	..
	Epinephrine, minims	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Quinidine, grains	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	..	..	..	3	..	..
	Attacks	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
3/25/47	Ephedrine, grains	..	..	..	..	..	..	..	..	¾*	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Epinephrine, minims	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Quinidine, grains	..	..	..	..	..	..	..	..	3	..	..	..	..	..	3	..	..	..	..	..	..	3	..	..	..
	Attacks	..	..	..	..	..	..	..	..	..	..	..	Faint feeling xx		..	..	..	..	..	..	..	..	..	..	..	..
3/26/47	Ephedrine, grains	..	..	..	..	..	..	..	..	..	¾†	..	..	¾†	..	..	..	¾†	..	..	..	¾†	..	..	..	¾†
	Epinephrine, minims	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1 cc.†	..	..	3	..	3	..
	Quinidine, grains	..	..	..	..	..	..	..	..	3	..	..	..	..	..	3	..	..	..	..	..	3	..	..	..	..
	Attacks	..	x	..	..	..	..	..	..	..	..	..	..	x	..	..	..	..		xxx	..	..	..	..	..	..
3/27/47	Ephedrine, grains	..	..	..	..	¾†	..	..	..	¾†	..	..	..	..	¾†	..	..	..	..	..	..	..	..	..	..	..
	Epinephrine, minims	..	3; 1 cc.	3	3	3	3	3	3	3	3	3	3	..	3	3	..	..	..	0.5 cc.		..	..	..	..	..
	Quinidine, grains	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	3	..	15 l. v.		3	5 l. v.	6
	Attacks	..	xx	..	..	..	..	..	..	..	..	..	xxxx	..	..	x	..	xxxx	xxx	xxxx	x	x	x x		x	..
3/28/47	Ephedrine, grains	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Epinephrine, cc.	..	..	..	..	1† 1‡	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Quinidine, grains	..	6¼ l. v.		6	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Attacks	xxxx		x		x§	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

* Orally.
† Intramuscularly.
‡ Into the heart.
§ x indicates Adams-Stokes attack.

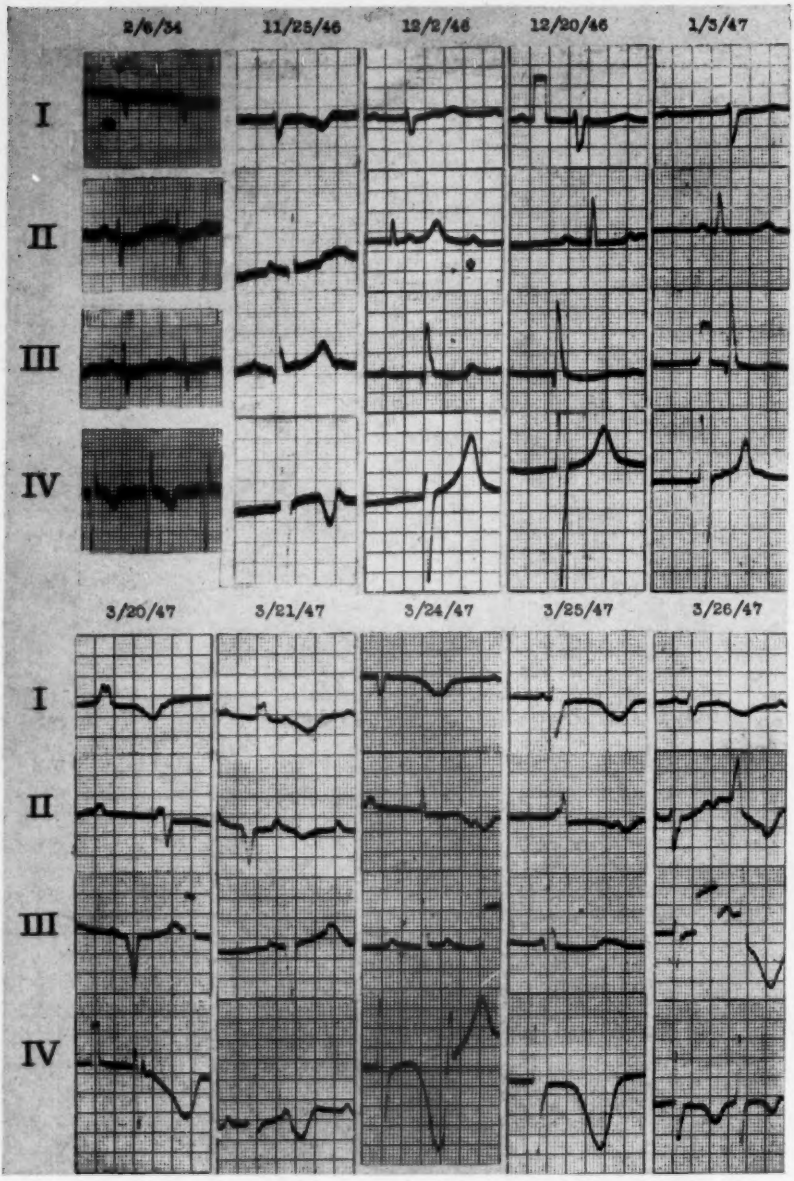

Fig. 1.—Feb. 6, 1934: Tracing made prior to first admission to hospital. Inverted T wave in Lead IV, normal (old-type connections); right axis deviation.

Remainder are interval tracings made during period of observation. Nov. 25, 1946 (first admission): Inverted T waves in Leads I and IV; right bundle branch block; anterior myocardial infarct. Dec. 2, 1946, Dec. 20, 1946, and Jan. 3, 1947: Right bundle branch block; complete heart block. Attack occurred on March 16, 1947. March 20 and 21, 1947 (second admission): Left bundle branch block; complete heart block; anterior myocardial infarct; inverted T waves in Leads I and IV. March 24 and 25, 1947: Inverted T waves in Leads I, II, and IV, with occasional premature ventricular contraction; right bundle branch block; anterior myocardial infarct; inverted T waves in Leads I and IV. March 26, 1947: Right bundle branch block; complete heart block; premature ventricular contraction; bigeminy; inverted T waves in Leads I and IV.

right bundle branch block with anterior myocardial infarction. Since ephedrine was given with apparent impunity during the previous hospitalization and epinephrine was given finally only after the onset of the seizures, these drugs probably played no part in initiating the attacks, but possibly increased their severity.

Representative electrocardiograms are presented (Fig. 1), including those taken prior to and during the first admission, during the interval period, and during the final admission when ventricular fibrillation was demonstrated.

The picture of complete heart block with changing right and left bundle branch block present in the serial tracings (Fig. 1) and in the tracings of March 27, 1947 (Fig. 2), may be explained by the following mechanisms: (1) idioventricular rhythm with pacemaker in the bundle of His with alternating right and left bundle branch block; (2) idioventricular rhythm with pacemaker below the His bundle producing ventricular rhythm, the ventricular center being located alternately in the right or left ventricle; when the origin is in the right ventricle, a picture of left

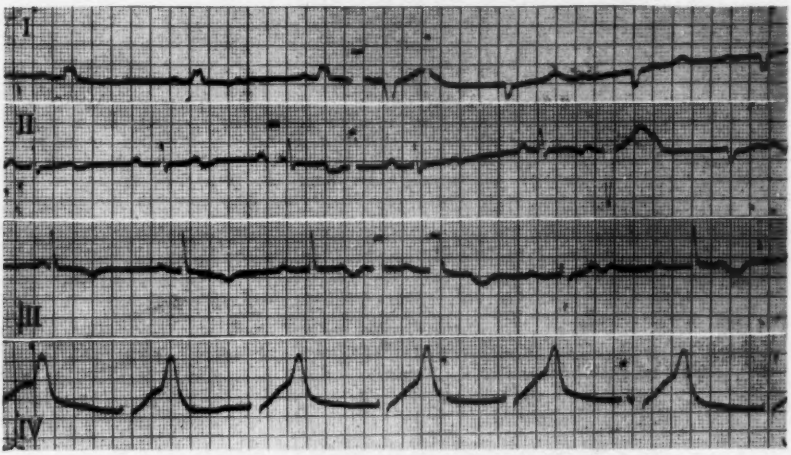

Fig. 2.—Tracing of March 27, 1947: Right and left bundle branch block; complete heart block; inverted T waves in Lead III. Left bundle branch block changing to right bundle branch block during time tracing was made.

bundle branch block is produced, and vice versa; idioventricular rhythm with pacemaker in the region of the bundle branch lesion above or below the level of the block, and (4) idioventricular rhythm with bilateral bundle branch block, the center being located below the lesion so that when the origin is in the right ventricle the picture of left bundle branch block is produced, and vice versa.

It is felt that the fourth mechanism with bilateral bundle branch block was the most likely possibility in the case presented. However, as Bain [1] has stated,

> Bilateral bundle branch block can be diagnosed with confidence when supraventricular impulses pass down each branch alternately. . . . When A-V block is complete the diagnosis is less certain, since it is possible for alternate right and left bundle branch block complexes to be due to the interplay of two ventricular centers, one above the lesion in a branch and the other below it.

1. Bain, C. W. C.: Variable Ventricular Complexes in Heart Block, and Their Relation to Bilateral Bundle Branch Block, Brit. Heart J. **3**:75-92 (April) 1941.

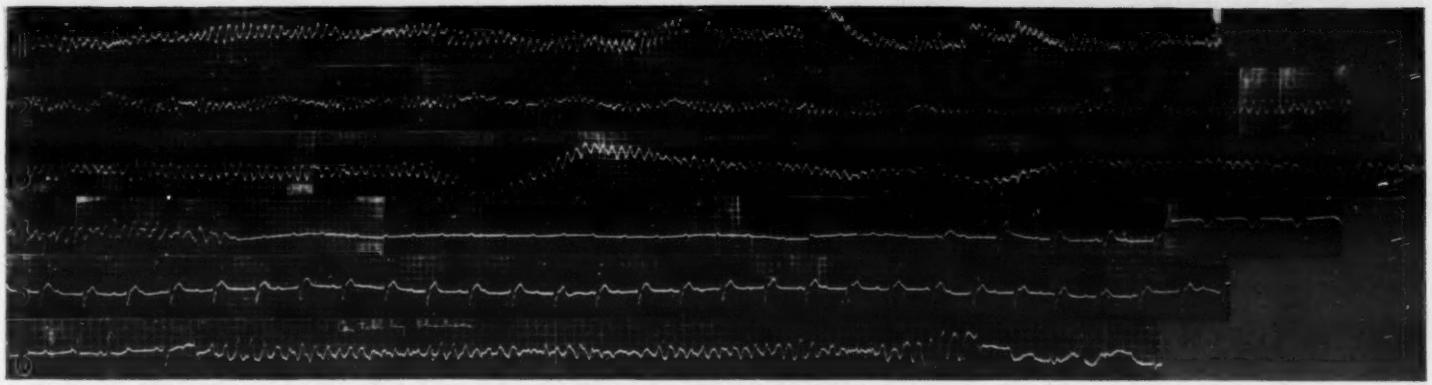

Fig. 3.—Lead II tracing made at 3 p. m., March 27, 1947. Tracings 1, 2, 3, 4, and 5 are continuous. This attack of venticular fibrillation lasted a little more than two minutes, ending with a period of ventricular asystole of 24 seconds' duration, as shown in part in Figure 4, tracings 2 and 3. At onset patient realized that an attack was coming on, stating that he felt "tight" and that he could not see. At end of one minute there was a loud cry with marked distortion of face. This was followed by period of apnea, during which he became very cyanotic. At end of two minutes patient gave a gasp, following which he became tonic, with generalized tonic and clonic convulsions. At end of approximately three minutes there was another gasp, and after four minutes patient was coming out of attack, with marked restlessness. As his breathing returned to normal, he became flushed and consciousness returned. However, patient showed marked paranoid tendency, attempting to strike and kick attending physicians.

Tracing 6 was made at 6: 38 p. m., March 27, 1947. During this attack of 17 seconds' duration, patient complained of transient blindness, but there was no definite loss of consciousness. Just preceding this attack there were frequent runs of prefibrillary ventricular tachycardia lasting four or five seconds, with 10 to 12 undulations. During these brief attacks patient did not lose consciousness, but sometimes complained of difficulty in vision.

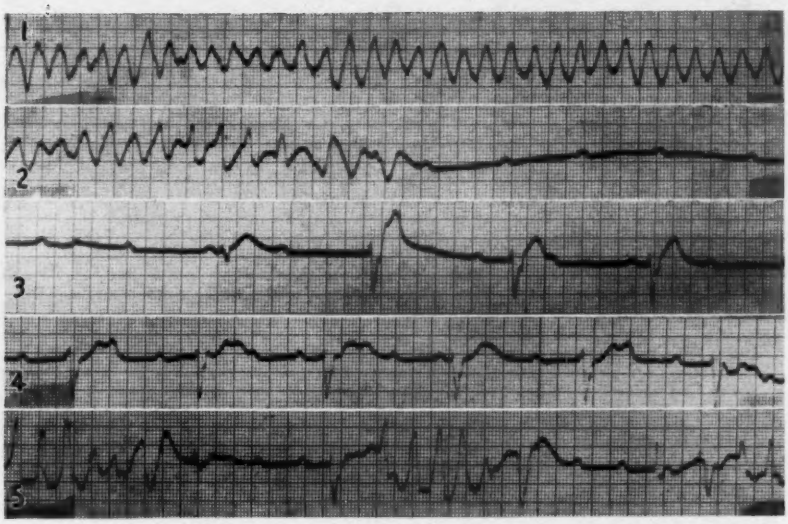

Fig. 4.—Tracings in Figures 4, 5, 6, and 7 represent excerpts from electrocardiograms taken during period of observed Adams-Stokes attacks before, during, and after intravenous administration of quinidine. Tracings are all of Lead II, not continuous, made March 27 and 28, 1947.

1. Tracing of ventricular fibrillation. Rate, 240 per minute, with variation in amplitude and form of complexes. Taken during attack of paroxysmal ventricular fibrillation shown in Figure 1 approximately one minute after onset.

2. Onset of period of ventricular asystole of 24 seconds' duration during attack shown in Figure 3. Auricular rate, 68 per minute.

3 and 4. Resumption of idioventricular rhythm after asystolic period of 24 seconds (not all this phase is shown). Left bundle branch block. Complete heart block. Ventricular rate, 38 per minute.

5. Onset of administration of quinidine intravenously. Tracing shows frequent runs of prefibrillary tachycardia lasting usually two to six seconds. There seemed to be definite depression of normal ventricular contractions. Idioventricular rhythm; rate, 43 per minute, with left bundle branch block.

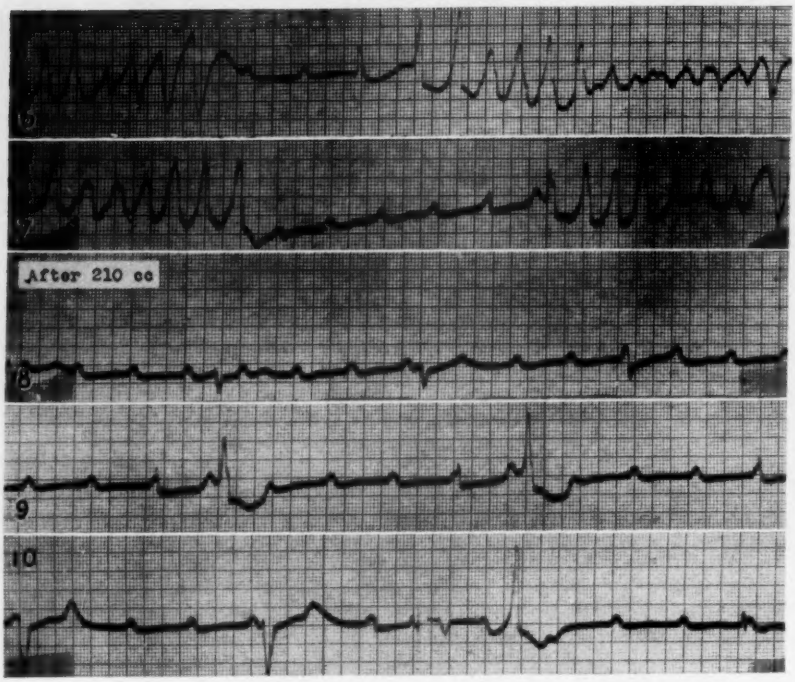

Fig. 5.—Continuation of Figure 4.

6. After administration of 130 cc. of quinidine sulfate (6.5 grains; 0.43 gm.) intravenously. Longer runs of prefibrillary ventricular tachycardia.

7. Prefibrillary ventricular tachycardia or flutter with intervening ventricular asystole of approximately three seconds' duration.

8. After administration of 210 cc. (10.5 grains; 0.7 gm.) intravenously of quinidine sulfate. Ventricular rate, 25 per minute. Auricular rate, 100 per minute.

9. Right bundle branch block with marked "suppression." Ventricular rate, 18 per minute. Auricular rate, 88 per minute.

10. Left bundle branch block followed by right bundle branch block. Auricular rate, 80 per minute. Ventricular rate, 22 per minute. Tracing taken at time that all the first 15 grains (1 gm.) of quinidine had been administered

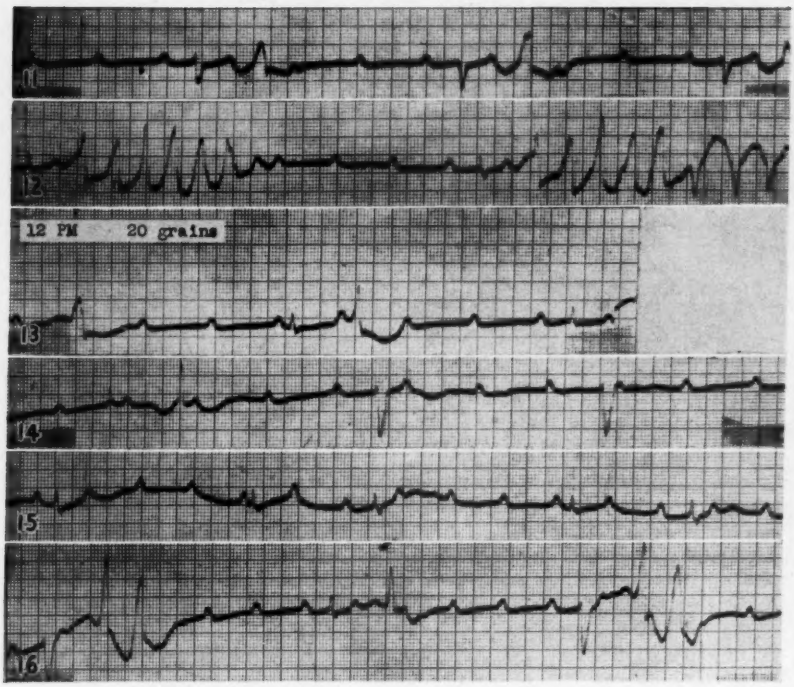

Fig. 6.—Continuation of Figure 5.

11. Left bundle branch block alternating with right bundle branch block. Auricular rate, 80 per minute. Ventricular rate, 40 per minute. Change in origin of beat.

12. Runs of prefibrillary ventricular tachycardia. Ventricular rate, 156 per minute, with intervening ventricular asystole.

13. Taken after second intravenous injection of 5 grains (0.3 gm.) of quinidine sulfate, making a total of 20 grains (1.2 gm.) given intravenously until about midnight. Auricular rate, 80 per minute. Ventricular rate, 18 to 34 per minute (?).

14. Same as 13. Auricular rate, 76 per minute. Ventricular rate, 24 per minute.

15. Same as 13. Auricular rate, 100 per minute. Ventricular rate, 30 per minute. Small complexes.

16. Taken before last injection of quinidine intravenously. Auricular rate, 104 per minute. Ventricular rate, 48 per minute. Multifocal "spasmodic" ventricular beats.

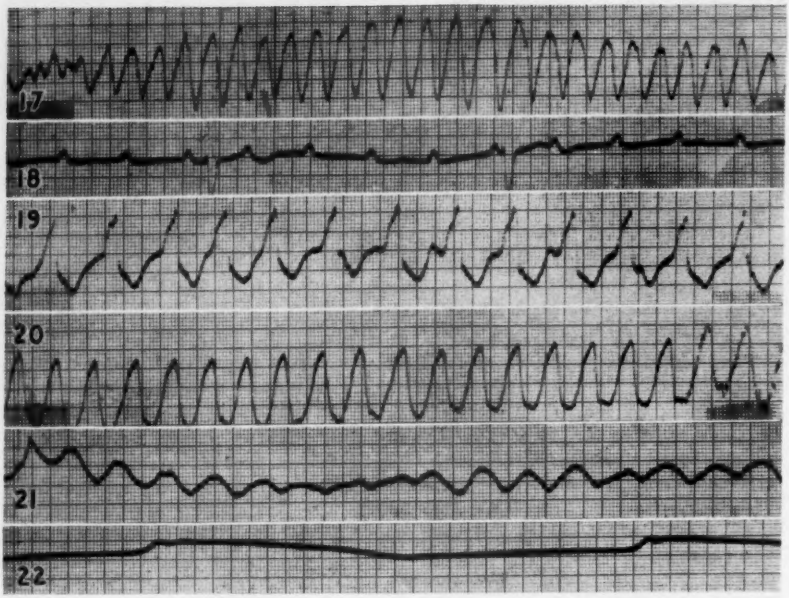

Fig. 7.—Continuation of Figure 6.

17. Same as 16. Prefibrillary ventricular tachycardia. Ventricular rate, 204 per minute.

18. Same as 16. Auricular rate, 90 per minute. Ventricular rate, 18 per minute. Complete heart block; left bundle branch block.

19. Taken just before terminal attack of ventricular fibrillation after last injection of 6¼ grains (0.41 gm.) of quinidine intravenously (total of 26¼ grains [1.70 gm.] intravenously). Ventricular rate, 96 per minute. Ventricular tachycardia.

20. Prefibrillary ventricular tachycardia. Ventricular rate, 145 per minute.

21. Ventricular fibrillation. Ventricular rate, 140 ± per minute.

22. Ventricular rate, 11 per minute (?). No auricular beats. Clinical death. Last two strips are excerpts from tracing made during final attack resulting in death.

It may now be possible to make the exact differential diagnosis of the above possibilities by reference to the spatial vectorcardiogram.

REVIEW OF LITERATURE

A review of the literature is outlined in Table 3.[2] An analysis of the 51 cases (including the case presented) reveals the following:

Reported Incidence.—The number of cases reported has averaged, since 1917, more than one case per year, more cases having been published in recent years probably because of the increased use of electrocardiography.

2. (*a*) Robinson, G. C., and Bredeck, J. F.: Ventricular Fibrillation in Man with Cardiac Recovery, Arch. Int. Med. **20**:725-738 (Nov.) 1917. (*b*) Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy, Heart **9**:269-281 (Dec.) 1922. (*c*) de Boer, S.: Über Kammerflattern und Kammerflimmern bei einem Patienten mit totalem Herzblock, Ztschr. ges. exper. Med. **32**:191-213 (July) 1923. (*d*) Willius, F. A.: Ventricular Fibrillation in Man with Temporary Cardiac Recovery, J. Lab. & Clin. Med. **8**:518-522 (May) 1923. (*e*) Donath, F., and Kauf, E.: Ventricular Fibrillation in Man, Wien. klin. Wchnschr. **37**:331-332 (April 3) 1924. (*f*) Gallavardin, L., and Bérard, A.: Un cas de fibrillation ventriculaire au cours des accidents syncopaux du Stokes-Adams, Arch. mal. cœur **17**:18-20 (Jan.) 1924. (*g*) Haines, S. F., and Willius, F. A.: Intermittent Ventricular Fibrillation with Complete Recovery, Boston M. & S. J. **193**:473-475 (Sept. 3) 1925. (*h*) von Hoesslin, H.: Kammerwühlen und Adams-Stokesscher Symptomkomplex, Klin. Wchnschr. **4**:62-64 (Jan. 8) 1925. (*i*) Levine, S. A., and Matton, M.: Observations on a Case of Adams-Stokes Syndrome Showing Ventricular Fibrillation and Asystole Lasting 5 Minutes, with Recovery Following Intracardiac Injection of Adrenalin, Heart **12**:271-275 (March) 1926. (*j*) Dock, W.: Transitory Ventricular Fibrillation as Cause of Syncope and Its Prevention by Quinidine Sulphate, Am. Heart J. **4**:709-714 (Aug.) 1929. (*k*) Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, ibid. **4**:559-572 (June) 1929. (*l*) Heimann, H. L.: The Mechanism of the Stokes-Adams Syndrome, Lancet **1**:68-71 (Jan. 12) 1929. (*m*) Shookhoff, C.: Ventricular Fibrillation with Cardiac Recovery, Caused by Carotid Sinus Pressure, in a Case of Auricular Fibrillation, Am. Heart J. **6**:758-767 (Aug.) 1931. (*n*) Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Electrocardiograms Obtained from a Patient with Auriculoventricular Dissociation and Recurrent Syncopal Attack, Arch. Int. Med. **49**:282-302, (Feb.) 1932. (*o*) Schwartz, S. P., and Jezer, A.: Transient Ventricular Fibrillation: The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient with Auriculoventricular Dissociation, ibid. **50**:450-469 (Sept.) 1932. (*p*) Freundlich, J.: Durch Kammerflattern ausgelöste Adams-Stokessche Anfälle, Deutsches Arch. klin. Med. **173**:617-624 (June) 1932. (*q*) Escamilla, R. F.: Report of a Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, Am. Heart J. **8**:850-857 (Aug.) 1933. (*r*) Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, ibid. **9**:792-801 (Aug.) 1934. (*s*) Lian, C., and Deparis, M.: Deux syncopes avec fibrillation ventriculaire transitoire dans un pouls lent permanent par dissociation auriculo-ventriculaire complète, Bull. et mém. Soc. méd. hôp. Paris **50**:569-575 (April 30) 1934. (*t*) Bizzozero, R. C.: Fibrilacion ventricular pasajera registrada durante una crisis sincopal en un sindrome de Stokes-Adams, Rev. argent. cardiol. **1**:371-379 (Nov.-Dec.) 1934. (*u*) Schwartz, S. P., and Hauswirth, L.: Studies on Transient Ventricular Fibrillation: Observations on Alterations in Rhythm of Heart Preceding Syncopal Seizures in Woman with Transient Auriculoventricular Dissociation, Am. J. M. Sc. **187**:478-488 (April) 1934. (*v*) Cahall, W. L.: Paroxysmal Ventricular Fibrillation, J. A. M. A. **105**:2054-2055 (Dec. 2) 1935. (*w*) Clerc, A., and Levy, R.: Sur la résistance du cœur chez certains malades en état de dissociation auriculo-ventriculaire permanente, Arch. mal. cœur **29**:307-334 (May) 1936. (*x*) Sigler, L. H.: Adams-Stokes Syndrome Induced by Transient, Recurrent Ventricular Fibrillation: Case

(Footnote continued on next page)

Incidence by Age.—In more than half of the cases (30) the syndrome occurred between the ages of 50 and 70 years, the range being 17 to 82 years.

Incidence by Sex.—Twenty-five patients were female and 21 male and for five patients the sex was not stated.

Incidence in Relationship to Cardiac Failure.—Cardiac failure was present in 17 patients and absent in 29. In five cases no mention was made of this condition.

Incidence in Relation to Conduction Defect.—Of the 50 cases in which intraventricular conduction was described, defects were present in 38, whereas in 12 normal conduction was present.

Prognosis.—In 48 of the 51 cases, the duration of survival was noted. For the 29 patients who died during the period of observation, the average survival period

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Report, Am. Heart J. **16**:109-116 (July) 1938. (*y*) Norris, G. W., and Landis, H. R. M.: Diseases of the Chest and the Principles of Physical Diagnosis, Ed. 6, Philadelphia, W. B. Saunders Company, 1938, pp. 208-209. (*z*) Gertz, G.; Kaplan, H. A.; Kaplan, L., and Weinstein, W.: Cardiac Syncope Due to Paroxysms of Ventricular Flutter, Fibrillation, and Asystole in a Patient with Varying Degrees of A-V Block and Intraventricular Block: Report of a Case, Am. Heart J. **16**:225-234 (Aug.) 1938. (*a'*) Sigler, L. H.: Fibrillatory Phase of Transient Recurring Ventricular Fibrillation, Internat. Clin. **1**:220-225 (March) 1939. (*b'*) Feil, H., and Rossman, P. L.: Electrocardiographic Observations in Cardiac Surgery, Ann. Int. Med. **13**:402-414 (Sept.) 1939. (*c'*) Torrey, R. G., and Leaman, W. G.: The Adams-Stokes Syndrome with Special Reference to the Electrocardiogram During Seizures, Tr. & Stud. Coll. Physicians, Philadelphia **6**:336, 1937. (*d'*) Fishberg, A. M.: Heart Failure, Ed. 2, Philadelphia, Lea & Febiger, 1940, p. 280. (*e'*) Parkinson, J.; Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack, Brit. Heart J. **3**:171-199 (July) 1941. (*f'*) Rakov, H. L.: Ventricular Fibrillation in Acute Coronary Artery Thrombosis During the Intravenous Administration of Quinidine Sulfate: Report of a Fatal Case, Ann. Int. Med. **16**:571-576 (March) 1942. (*g'*) O'Farrell, P. T.: Ventricular Fibrillation in Stokes-Adams Syndrome, Irish J. M. Sc. **6**:591-597 (Nov.) 1943. (*h'*) Zimdahl, W. T., and Fulton, F. T.: Transient Ventricular Fibrillation: Report of Case with Spontaneous Recovery, Am. Heart J. **32**:117-124 (July) 1946. (*i'*) Parsonnet, A. E.; Berstein, A., and Klosk, E.: Ventricular Fibrillation with Special Reference to the Morgagni-Adams-Stokes Syndrome: Report of an Unusual Case, ibid. **31**:769-779 (June) 1946. (*j'*) Schnur, S.: Newer Concept of Stokes-Adams Syndrome, ibid. **35**:298-308 (Feb.) 1948. (*k'*) Bechgaard, P.: Paroxysmal Ventricular Fibrillation with Recovery, Acta med. scandinav. **132**:9-19, 1948. (*l'*) Schwartz, S. P.; Orloff, J., and Fox, C.: Transient Ventricular Fibrillation: The Prefibrillary Period During Established Auriculoventricular Dissociation with a Note on the Phonocardiograms Obtained at Such Times, Am. Heart J. **37**:21-35 (Jan.) 1949. (*m'*) Moe, T.: Morgagni-Adams-Stokes Attacks Caused by Transient Recurrent Ventricular Fibrillation in Patient Without Apparent Organic Heart Disease: Case Report, ibid. **37**:811-819 (April) 1949. (*n'*) Storstein, O.: Adams-Stokes Attacks Caused by Ventricular Fibrillation in a Man with Otherwise Normal Heart, Acta med. scandinav. **133**:437-441, 1949. (*o'*) Daniel, F. D., and Magruder, R. G.: Report of a Case of Ventricular Fibrillation with Recovery Following Acute Coronary Occlusion, Am. Heart J. **39**:451-454 (March) 1950. (*p'*) Scott, R. W., and Sancetta, S. M.: Stokes-Adams Attacks Induced by Rectal Stimulation in a Patient with Complete Heart Block, Circulation **2**:886-889 (Dec.) 1950. (*q'*) Gold, H.: Quinidine in Disorders of the Heart, New York, Paul B. Hoeber, Inc., 1950, p. 72. (*r'*) Pastor, B. H., and Worrilow, S. H.: Electrocardiographic Patterns in Stokes-Adams Syndrome, Ann. Int. Med. **34**:80-89 (Jan.) 1951. (*s'*) Enselberg, C. D.; Croce, J. P., Jr., and Lown, B.: Ventricular Fibrillation Due to Digitalis Preparations: Review and Report of 2 Cases Following Intravenous Administration of Acetyl Strophanthidin, Circulation **3**:647-657 (May) 1951. (*t'*) Gonin, A.; Gallavardin, L.; Froment, R., and Finas, C.: À propos de 3 cas de syncopes de "Morgagni-Adams-Stokes" par fibrillation ventriculaire, Arch. mal. cœur **44**:398-406 (May) 1951.

TABLE 3.—*Summary of Cases from Literature**

Case No.	Author	Year	Sex	Age	Failure	Past History	Electrocardiogram	Observed Attacks	Medications	Outcome
1	Robinson & Bredeck [2a]	1917	F	45	+	Recurrent rheumatic fever	Normal mechanism with left-sided predominance; later defective IVC and HB	3	Strophanthin	Died after 30 hr.
2	Kerr & Bender [2b]	1921	M	68	+	Failure, digitalis, 4 yr.; dizzy spell; BP 220/75	CHB, AF, DVC, RBBB, VF, and VST with attack	6	Quinidine aggravated; 3.6 gm. in 4 days	9 mo., transient faintness; survived 7 yr., no further attacks
3	Willius [2d]	1923	M	44	+	Digitalis; A-S attacks	PVC, DIC, VF	1	Spontaneous recovery in 10 sec.	Died 34½ hr. after attack; PM: extensive myocardial damage
4	de Boer [2c]	1923	F	60	0	Nephritis	CHB	Several	None	Died after 2 mo. in attack
5	Donath & Kauf [2e]	1924	..	..	..	A-S attacks	VF	..	? Attacks disappeared after thorough emptying of bowels	.....
6	Gallavardin & Bérard [2f]	1924	F	55	0	A-S attacks 4 yr.	CHB, VR, 35-42; AR, 85	Several	None	Survived period of observation
7	Haines & Willius [2g]	1925	F	65	+	Exophthalmic goiter treated with strong iodine solution; AF	AF	1	Epinephrine, 5 m. subcutaneously (1:1,000); slowly regained consciousness	Recovered
8	von Hoesslin [2h]	1925	F	31	0	Slow pulse	CBH, VR, 32-34; ES, VF with VST with attack	..	.....	.....
9	Levine & Matton [2i]	1926	F	52	+	1 or 2 attacks daily for 1 yr.	CHB, RBBB, VST with attack, 79 sec.	9	No quinidine; intracardiac epinephrine with benefit ?	Died of attack ? 1 mo. after discharge
10	Dock [2j]	1929	M	36	0	For 6 or 8 mo., once a month to 1 or more a day	Normal; rare VES	Several	Attack precipitated by epinephrine i. v.; helped by quinidine	Survived at least 1 yr.
11	Davis & Sprague [2k]	1929	F	48	+	Failure for 1½ yr.; no A-S attacks	AF and ventricular ectopic beat	"Many" 48 ?	Digitalis, then quinidine, then digitalis; quinidine 8.2 gm. in 4 days; aggravated by quinidine	Died after about 1 mo.; observed 8 hr. after onset of attacks
12	Heimann [2l]	1929	F	46	+	Hypertension	Partial HB, RBBB, CHB	..	Barium chloride, epinephrine no benefit	Died during attack 6 wk. after onset
13	Shookhoff [2m]	1931	M	58	+	6 mo.	AF	..	Carotid pressure, brief period of VF	Improved; no further attacks
14	Schwartz [2n]	1932	F	66	+	Attacks for 1 yr., up to 30 in 1 day; BP 280/80	CHB	6 in 7 mo.	No quinidine; saturated solution KI, no effect	Died after 7-mo. observation
15	Schwartz & Jezer [2o]	1932	F	65	+	Seizures for 6 mo.; BP 170/60	Complete AV dissociation	207 in 1 day	By others, barium chloride, epinephrine, worse; by authors, no drug	Survived 4 mo. +
16	Freundlich [2p]	1932	F	69	0	BP 250/70	CHB, VR, 48, ES, ? VF, coronary, right; VF with VST with attack	..	.....	Attacks ceased
17	Escamilla [2q]	1933	M	66	0	Fainting spells 2 yr.	SR with coupling due to PVC; no conduction damage	..	Quinidine used intermittently over long period to 7 mo., of questionable value	Survived period of observation
18	Schwartz & Jezer [2r]	1934	M	17	0	Infectious myelitis, 5 wk.	SR	Several	Epinephrine, no help	Died in attack 2 days after onset
19	Lian & Deparis [2s]	1934	F	51	0	A-S 2 yr.; BP 220/90	CHB; VR, 35; AR, 78; partial RBBB, VST	Many	.....	Died during attack

TABLE 3.—*Summary of Cases from Literature*—Continued*

20	Bizzozero [2t]	1934	F	60	+	A-S 1 mo.; diabetes	CBH; VR, 40; AR, 110; partial RBBB	..	.....	.....
21	Schwartz & Hauswirth [2s]	1934	F	56	0	A-S 6 mo.; BP 230/120; cholecystitis	CHB, 3:2 HB, RBBB	..	.....	Died after 1 yr. with syncope
22	Cahall [2r]	1935	M	68	0	A-S 3 days; BP 200/100	CHB, PVC	..	Quinidine aggravated	Died after 6 wk. in attack
23	Clere & Levy [2w]	1936	F	75	0	A-S 9 yr.	CHB; VR, 32; RBBB	..	.....	Alive after 10 mo., few attacks
24	Sigler [2x]	1938	M	58	0	Angina pectoris, A-S for months	3:2 HB	Several	Quinidine and epinephrine aggravated; 50 cc. 50% dextrose helped	Died in attack 6 wk. after 1st attack
25	Norris & Landis [2y]	1938	..	..	..	.....	CHB, VF, A-S	Several	.....	Died after 2 days
26	Gertz & others [2z]	1938	F	59	+	Hypertension; BP 260/90; A-S for years	Partial AV block and IV block	6	Quinidine orally; 9 gr. quinidine i. v. no benefit ?; epinephrine	Died 12th day while receiving quinidine i. v.; PM: heart only, atherosclerosis
27	Sigler [2a']	1939	F	66	0	Diabetes; CT; A-S 6 mo. later; angina	CHB	..	Helped by epinephrine ?; 50 cc. dextrose i. v. helped	Died in attack after 5 wk.
28	Feil & Rossman [2b']	1939	F	42	0	Constrictive pericarditis; operation	Operation produced paroxysm of VF	0	7 gr. quinidine preoperatively	Recovered spontaneously
29	Torrey & Leaman [2c']	1939	..	..	..	.....	CHB	..	.....	.....
30	Fishberg [2d']	1940	..	..	..	.....	CHB	..	.....	.....
31	Parkinson & others [2e']	1941	F	62	0	Hypertension; A-S 6 wk. before admission	2:1, 3:1 block, CHB, LBBB, RBBB	Many	Epinephrine, no effect ?	Survived period of observation
32	Rakov [2f']	1942	M	57	0	Acute coronary occlusion with anterior infaret	.....	2 to 3	.....	Death in VF
33	O'Farrell [2g']	1943	F	64	0	BP 300/120; attacks of dizziness	CHB	Several	Quinidine, 3 gr. q. 4 hr., no dramatic effect	Died after approximately 1-mo. observation
34	Zimdahl & Fulton [2h']	1946	M	66	0	Pneumonia treated with sulfadiazine	Acute myocardial infarction, RBBB	15	Pentylenetetrazole, quinidine, no aggravation	Discharged from hospital after 37 days; symptom free
35	Parsonnet & others [2i']	1946	F	73	0	1st attack 5 yr. previously	Complete AV block	Several	Phenobarbital; papaverine	In good health almost 7 yr. after 1st observed attack; patient refuses treatment
36	Schnur [2j']	1948	F	70	0	Convulsions for 24 hr.	Complete AV block, VF, VT, V asystole	Many	Ephedrine, quinidine, worse; epinephrine, disappearance of attacks	Died of cerebral accident 7th hospital day; PM: coronary arteriosclerosis
37	Bechgaard [2k']	1948	M	50	0	Many yr.; onset with Rx for tapeworm: extract of fern	Rheumatic fever with fits	..	Strophanthin, 0.25 mg. i. v., better?	Dropped dead 13 mo.; PM: heart normal
38	Schwartz & others [2l']	1949	F	52	+	For 6 mo. recurrent periods of unconsciousness	CHB; atropine produced SR	"100" per day	Digitalis and ephedrine, neither prevented attacks	Died 3½ mo. after admission
39	Schwartz & others [2l']	1949	M	49	+	For 6 yr. recurrent black-outs; aortic insufficiency	CHB	Many	Ephedrine, no effect; many forms of therapy tried	Still under observation

Case No.	Author	Year	Sex	Age	Failure	Past History	Electrocardiogram	Observed Attacks	Medications	Outcome
40	Schwartz & others [21]	1949	M	62	0	For 9 wk. attacks of blindness; high BP for 20 yr.	CHB	Numerous	Numerous drugs, none effective	Died in attack 5 mo. after admission
41	Moe [2m]	1949	M	38	0	Attacks of palpitation; no organic heart disease or HB	SR, VF	16	Epinephrine, 5 spontaneous attacks; later quinidine 1 gm. in 7 hr., then 0.2 gm. a day	In good health on 0.2 gm. quinidine t. i. d.; stopped drug and had recurrence; 0.1 gm. b. i. d. and later 0.1 gm. a day; OK after 3 yr.; ECG normal
42	Storstein [2a]	1949	M	37	0	PVC for 5 yr.; vertigo; dizziness	Normal between attacks, VF with attacks, no asystole	Several	Amphetamine, epinephrine, ephedrine, attacks subsided, no aggravation; induced vomiting by patient stopped attacks	Survived 4 yr. +
43	Daniel & Magruder [2o]	1950	M	58	0	Attack of syncope 2 yr. previously; acute posterior infarct	Acute posterior infarct	1	Epinephrine, caffeine and sodium benzoate; artificial respiration for attack; later quinidine, 18 gr. a day for 30 days; no recurrence	Recovery
44	Scott & Sancetta [2p]	1950	F	62	0	Syncopal attacks for 2 wk.	CHB, VT, VF	Several induced by rectal stimulation	Ephedrine before ECG made, then quinidine, questionable benefit	Death after 12 hr.; PM: coronary sclerosis
45	Gold [2q]	1950	..	..	..	.....	.....	Several	Quinidine, no value	Recovery 2 yr. +
46	Pastor & Worrilow [2r]	1951	M	82	0	Exertional dyspnea 3 mo. before, no pain; LUQ and left arm discomfort; impression of myocardial infarction	AF and PVC, LBBB, CHB; PVT with periods of asystole	Many over 2-hr. period	Quinidine, 6 gr. at once and repeated once in 6 hr., aggravation?	Death with PVT about 12 hr. after onset; PM: fibrosis, sclerosis at base of aortic valve and septum; no infarct
47	Enselberg & others [2s]	1951	M	70	+	Arteriosclerotic thyrotoxic heart disease	Auricular flutter with 2:1 AV block; acetyl strophanthidin I. v.; supraventricular tachycardia	1	.....	Death 17 min. after injection; PM: recent infarct left ventricle and septum, coronary sclerosis
48	Enselberg & others [2s]	1951	M	56	+	Angina 8 yr.	QRS 0.12 sec.; anterior infarct; acetyl strophanthidine I. v.	1	.....	Recovery from attack in 45 min.; died 15th hospital day; old anterior and posterior infarcts; coronary sclerosis
49	Gonin & others [2t]	1951	M	52	0	A-S attacks 4 yr.	CHB, VF	..	.....	Died suddenly after 13 mo.
50	Gonin & others [2t]	1951	F	55	+	Hypertension	CHB	Many	Onset after digitalis orally; helped (?) by nitrites, aminophyllin, and atropine	.....
51	Robertson & Mathews	1952	M	64	0	.....	CHB, RBBB, LBBB, VT, VF, VST	50+	Ephedrine, quinidine orally and then I. v.; quinidine aggravated?	Died in VF; PM: coronary sclerosis

* Plus sign indicates presence, 0, absence, of cardiac failure. AF means auricular fibrillation; AR, auricular rate; A-S, Adams-Stokes; AV, auriculoventricular; BP, blood pressure; CHB, complete heart block; CT, coronary thrombosis; DIC, defective intraventricular conduction; DVC, defective ventricular conduction; ES, extrasystoles; HB, heart block; IV, intraventricular; i. v., intravenously; IVC, intraventricular conduction; LBBB, left bundle branch block; PM, postmortem examination; PVC, premature ventricular contraction; PVT, prefibrillary ventricular tachycardia; RBBB, right bundle branch block; SR, sinus rhythm; V, ventricular; VES, ventricular extrasystole; VF, ventricular fibrillation; VR, ventricular rate; VST, ventricular standstill, and VT, ventricular tachycardia.

was nine weeks, ranging from one hour to seven years. For the 19 who survived, the period of observation ranged from two days to more than seven years.

Therapy.—1. Quinidine: The effect seemed to correlate with the state of conduction, so that those with defective intraventricular conduction showed evidence of aggravation, while those with normal conduction usually were benefited. Specifically, of 10 patients with defective conduction, the condition in 6 was aggravated and 4 showed no effect. Of seven with normal conduction, four were benefited, two showed aggravation, and one showed no effect.

2. Digitalis: Four of five patients with definite conduction defect given digitalis showed aggravation, whereas one showed no effect. One patient with normal conduction was benefited.

3. Epinephrine and/or Ephedrine: No special effect was noted in the analysis. Of 10 patients with defective conduction, 3 seemed benefited, the condition in 2 was aggravated, and 5 showed no effect. Of six with normal conduction, one seemed benefited, three showed aggravation, and two showed no effect.

4. Barium Chloride: One patient with defective conduction showed no effect.

5. Saturated Solution of Potassium Iodide: One patient with defective conduction showed no effect.

6. Fifty per Cent Dextrose Solution Given Intravenously: Two patients with defective conduction showed benefit.

7. Phenobarbital with Papaverine: One patient with defective conduction showed benefit.

8. Spontaneous Effects: Spontaneous recovery was noted in two patients with defective conduction. In one patient with normal conduction, induced vomiting seemed to stop the attacks.

9. Miscellaneous: One patient was helped by aminophyllin, atropine, and nitrites, and the condition of another was not aggravated by amphetamine (benzedrine®)

No therapy was stated in 12 cases (11 with defective conduction and 1 with normal conduction).

In two cases with defective conduction, spontaneous recovery was noted.

Present Concepts Concerning Adams-Stokes Syndrome Due to Transient Ventricular Fibrillation.—A. Definition: The Adams-Stokes syndrome is characterized by recurrent attacks of unconsciousness, often accompanied with muscular twitching or generalized convulsions. Although this has been thought to occur in patients with complete heart block, chiefly when the ventricular diastole is prolonged so as to produce cerebral ischemia, it now is apparent that paroxysmal rapid heart action (including ventricular tachycardia, prefibrillary ventricular tachycardia or "ventricular flutter," and ventricular fibrillation) is commonly the underlying mechanism.

B. Clinical Pattern: If the circulation is impaired for only six to eight seconds, the patient is aware of only a sensation of darkness before the eyes. If, however, the duration is 10 seconds or more, consciousness usually is lost, with onset of pallor, upturning of the eyes, stertorous respiration giving way to apnea, and twitching of the arms and legs, followed by tonic-clonic convulsions with marked cyanosis, often accompanied with incontinence of urine and feces. The pulse cannot be felt,

nor can heart sounds be heard, the latter being substantiated by the absence of acoustic vibrations in the phonocardiogram.[2f] Impaired circulation over four to five minutes is usually fatal, although spontaneous revival after six minutes has been reported.[3] Spontaneous return to consciousness is associated with flushing, followed by paranoid tendency and incoherence with clouded sensorium. As many as 300 attacks, lasting 50 seconds to three minutes, were recorded in one patient in a 24-hour period.[3]

C. Electrocardiographic Findings: An electrocardiogram should be made in all cases of Adams-Stokes seizures in order to identify positively the underlying mechanism. The electrocardiographic findings are those of continuous oscillations, irregular in form and rate. Sigler [2a] describes two stages of the fibrillary phase: the first showing complexes resembling paroxysmal ventricular tachychardia but differing in that considerable variation is present in the voltage and appearance of contiguous complexes; the second showing sudden rise in rate and marked variation in voltage and appearance so that no two complexes seem alike. The term, prefibrillary ventricular tachycardia, or so-called ventricular flutter, has been used and the details of the findings have been described by Schwartz.[4] However, even the short runs of prefibrillary ventricular tachycardia are considered to represent true ventricular fibrillation. Although recurrent ventricular fibrillation, associated with ventricular standstill, has been recorded in 20 cases,[2e] it is likely that if continuous tracings could be made periods of asystole following ventricular fibrillation would be found to be common. However, in such instances, as White [5] warns, the therapy should be directed toward the ventricular fibrillation rather than the asystole. Interval electrocardiograms often indicate complete heart block, but paroxysmal ventricular fibrillation has been reported in persons showing normal interval tracings.

D. Physiology: The usual concept of ventricular fibrillation involves the circus movement theory of Lewis. However, in 1928, Scherf [6] demonstrated that circus movement could not be the mechanism underlying auricular flutter and fibrillation. More recently, Prinzmetal [7] stated that to date he has found no cinematographic or electrocardiographic evidence supporting the circus movement mechanism in the ventricles. The evidence indicates that ventricular fibrillation has its origin from a single, very rapidly discharging focus in much the same manner as auricular fibrillation. Wiggers [8] stated that during ventricular fibrillation arterial pressure falls abruptly to very low levels and death results in six to eight minutes from anemia of the brain and spinal cord.

3. Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Fibrillary Process and Its Development in Man, J. Mt. Sinai Hosp. **8**:1005-1020 (Jan.-Feb.) 1942.

4. Schwartz, S. P.: Studies on Transient Ventricular Fibrillation: III. The Prefibrillatory Mechanism During Established Auriculo-Ventricular Dissociation, Am. J. M. Sc. **192**:153-163 (Aug.) 1936.

5. White, P. D.: Heart Disease, Ed. 2, New York, The Macmillan Company, 1939, pp. 667 and 683.

6. Scherf, D.: Versuche zur Theorie des Vorhofflatterns und Vorhofflimmerns, Ztschr. ges. exper. Med. **61**:30-44, 1928; abstracted, Ztschr. Kreislaufforsch. **20**:432-436 (July 15) 1928.

7. Prinzmetal, M.: Personal communication to the authors.

8. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, Am. Heart J. **20**:339-412 (Oct.) 1940.

E. Pathology: Paroxysmal ventricular tachycardia usually occurs in persons with serious heart disease caused by coronary arteriosclerosis, often complicated by complete heart block. However, attacks have been reported in persons with no clinical or postmortem evidence of organic heart disease. Thompson [9] has stated that the bundle of His is especially vulnerable in the atherosclerotic age group, in which 80 to 90% of complete atrioventricular heart block occurs. Kay [10] found that in coronary heart disease complete heart block is usually associated with obstruction of the posterior blood supply and occurs oftener in posterior than in anterior infarct. According to Schnur,[2f] a partially inadequate vascular supply to the auriculoventricular bundle, because of its unusual sensitivity to anoxemia, may result in total functional impairment without causing demonstrable histologic change. Sigler [11] reported that there appear to be local circulatory stasis and edema of the auriculoventricular node, the bundle, and bundle branches, resulting in sudden interference with nutrition and oxygenation.

F. Etiology of Paroxysmal Ventricular Fibrillation: Probably the commonest etiological factor in the production of clinical ventricular fibrillation is coronary arterial disease. It is particularly likely to occur after sudden occlusion of the coronary vessels, producing anoxia and ischemia. The presence of intraventricular conduction defects, particularly complete heart block, seems to be of considerable etiological significance. Schwartz and associates [12] showed that anoxia may result in transient auriculoventricular dissociation and ventricular fibrillation in patients subject to transient ventricular fibrillation. According to Wiggers and co-authors,[13] ischemia itself causes significant and variable decrease in the threshold of sensitivity to ventricular fibrillation produced experimentally by electric shock. The use of certain toxic drugs, particularly in susceptible persons, intravenously and in large doses definitely tends to favor the development of ventricular fibrillation. Rakov [2f] concluded that anything which depresses the normal regulatory function of the Tawara-His-Purkinje system on the ventricular myocardium, such as quinidine, may produce ventricular fibrillation. Craver and colleagues [14] produced ventricular fibrillation by the intravenous injection of mercurial diuretics in dogs. Kayden and co-workers [15] indicated that too-rapid intravenous administration of procaine amide

9. Thompson, I.: Ventricular Fibrillation Causing Sudden Death of a Patient with Disease of Left Coronary Artery, J. A. M. A. **116**:2583-2585 (June 7) 1941.

10. Kay, H. B.: Ventricular Complexes and Heart Block, Brit. Heart J. **10**:177-187 (July) 1948.

11. Sigler, L. H.: Treatment of Stokes-Adams Syndrome by Hypertonic Glucose Solution Given Intravenously, Ann. Int. Med. **13**:101-106 (July) 1939.

12. Schwartz, S. P.; Leiner, G. C., and Michtom, R. J.: Transient Ventricular Fibrillation: II. The Effects of Gradually Induced Oxygen Deficiency on Patients with Transient Ventricular Fibrillation and on Patients with Periodic Standstill of the Ventricle, Am. Heart J. **37**:918-926 (May) 1949.

13. Wiggers, C. J.; Wégria, R., and Pinera, B.: Effects of Myocardial Ischemia on Fibrillation Threshold: Mechanism of Spontaneous Ventricular Fibrillation Following Coronary Occlusion, Am. J. Physiol. **131**:309-316 (Dec.) 1940.

14. Craver, B. N.; Yonkman, F. F., and Rennick, B. R.: Antidotes to Ventricular Fibrillation Induced by Mercurial Diuretics, Am. Heart J. **40**:590-594 (Oct.) 1950.

15. Kayden, H. J.; Brodie, B. B., and Steele, J. M.: Use of Procaine Amide in Cardiac Arrhythmias, Mod. Concepts Cardiovas. Dis. **20**:100-101 (June) 1951.

("pronestyl") has produced ventricular fibrillation. DiPalma [16] reported that intravenous administration of calcium salts for estimation of circulation time or for other reasons has resulted in sudden death, presumably because of ventricular fibrillation. Enselberg and associates,[2a] stated that giving the full intravenous dose of digitalis to patients with recent myocardial infarction may provoke ventricular fibrillation. Schwartz and Jezer [17] have produced prefibrillary arrhythmia in patients with complete heart block with ouabain and digifolin given intravenously. Wégria [18] listed other drugs as capable of producing ventricular fibrillation, particularly when given intravenously to persons with conduction defects, namely, potassium chloride, procaine hydrochloride, and papaverine hydrochloride. According to Feil and Rossman,[2b] in cardiac surgery ventricular fibrillation at operation or postoperatively is "the constant fear of the surgeon."

Wiggers [8] stated that ventricular fibrillation is apparently the cause of sudden death following inhalation of chloroform, benzene, cyclopropane, and other vapors. It may prove to be, more frequently than has been suspected, the cause of sudden death after severe blows upon or other trauma to the chest, with or without obvious injury to the heart. Ventricular fibrillation also probably occurs in cases of stab or bullet wounds in which death is not the result of cardiac hemorrhage. However, the commonest causes of human ventricular fibrillation are sudden occlusion of coronary vessels, usually due to thrombosis, and electric shock, including electrocution and accidental shock, as from household appliances. Chenoweth [19] stated that in order for cyclopropane or chloroform to induce ventricular fibrillation elevated circulating concentration of epinephrine is required, as by anxiety or injection. Many hydrocarbons, including gasoline, may also sensitize the ventricles to epinephrine; hence, the hazard of injection of epinephrine to accident victims exposed to gasoline vapors and the danger of anxiety in persons in vehicle interiors, such as automobiles or aircraft.

G. Incidence: Ventricular fibrillation has been considered to be a common terminal occurrence in persons dying suddenly, as in acute myocardial infarction or ventricular dilatation due to cardiac failure. Thompson [9] in 1941 reported the seventh instance of proved ventricular fibrillation occurring as the terminal cardiac action in a patient with disease of the coronary artery. Beck and co-authors [20] have stated that ventricular fibrillation is the terminal arrhythmia in approximately 50% of patients.

Adams-Stokes attacks formerly had been considered to be caused almost exclusively by ventricular slowing or standstill, occurring in persons having complete

16. DiPalma, J. R., and Schults, J. E.: Antifibrillatory Drugs, Medicine **29**:123-168 (May) 1950.

17. Schwartz, S. P., and Jezer, A.: Effects of Intravenous Administration of Digitalis Bodies on Patients with Transient Ventricular Fibrillation, Am. Heart J. **16**:462-468 (Oct.) 1938.

18. Wégria, R.: Ventricular Fibrillation in Medical Physics, edited by O. Glasser, Chicago, The Year Book Publishers, Inc., 1944, Vol. 1, pp. 442-446.

19. Chenoweth, M. B.: Ventricular Fibrillation Induced by Hydrocarbons and Epinephrine, J. Indust. Hyg. & Toxicol. **28**:151-158 (July) 1946.

20. Beck, C. S.; Pritchard, W. H., and Feil, H.: Ventricular Fibrillation of Long Duration Abolished by Electric Shock, J. A. M. A. **135**:985-986 (Dec. 13) 1947.

auriculoventricular block. However, as Katz [21] stated, it is not sufficiently recognized that Adams-Stokes seizures sometimes are due to paroxysms of rapid heart action rather than to ventricular standstill. Parkinson and co-workers [2e] found that only 55% of Adams-Stokes attacks were associated with ventricular asystole, the remainder being due to various combinations of ventricular tachycardia, ventricular fibrillation, and ventricular asystole. Moe [2m] reported that many investigators now feel that Adams-Stokes attacks are equally often, or even oftener, the result of ventricular tachycardia or ventricular fibrillation. Sigler [2n] found 17 cases of paroxysmal ventricular fibrillation reported to 1939. Schwartz [3] found that 36 patients with paroxysmal ventricular fibrillation had been described in the literature up to 1942. Scherf and Boyd [22] stated that Adams-Stokes attacks due to ventricular tachycardia and fibrillation, formerly regarded as rare, are in reality common. However, probably few clinicians have observed more than one or two cases. Gold [2q] stated that he has seen only one case of paroxysmal ventricular fibrillation.

H. Diagnosis: The diagnosis is usually established by means of an electrocardiogram taken during an attack. However, tracings made between attacks may be of definite value in suggesting the diagnosis. Schwartz and Jezer[20] described in patients with auriculoventricular dissociation marked depression of conduction in the ventricles prior to the onset of ventricular fibrillation. These authors also showed that in patients with auriculoventricular dissociation small doses of epinephrine given during the free intervals produced only acceleration of the basic idioventricular rate in those whose attacks were due to standstill, whereas short recurrent periods of ventricular excitation were produced in those whose attacks were the result of transient ventricular fibrillation. Schwartz and associates [2r] stated that a clinical diagnosis of transient ventricular fibrillation may be suspected in patients with auriculoventricular dissociation if preceding the period of unconsciousness the heart rate has been noted to increase above the usual basic rate. DiPalma and Schults [16] maintained the Adams-Stokes seizures due to transient ventricular fibrillation are preceded by ventricular premature beats in many, or perhaps in most, instances. Levine and Harvey [23] reported that in ventricular tachycardia and flutter heart sounds are audible, whereas in ventricular fibrillation no heart sounds can be heard.

I. Prognosis: Katz [24] expressed the opinion that the expectation of life is seldom more than a year or two in complete heart block with widened QRS complexes. O'Farrell [2g] stated that in transient ventricular fibrillation the outlook is very grave, since most patients already have serious myocardial disease and seldom survive more than a few weeks or a month after the initial onset of the irregularity. Schwartz [3] stated that two patients were known to have lived four and one-half years each, during which time they experienced numerous seizures of transient ventricular fibrillation, with death in one of these attacks. While the prognosis is always grave, it is

21. Katz, L. N.: Exercises in Electrocardiographic Interpretations, Philadelphia, Lea & Febiger, 1946, p. 262.

22. Scherf, D., and Boyd, L. J.: Cardiovascular Disease, Philadelphia, J. B. Lippincott Company, 1947, pp. 318-322.

23. Levine, S., and Harvey, W. P.: Clinical Auscultation of the Heart, Philadelphia, W. B. Saunders Company, 1949, p. 119.

24. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941, p. 262.

significant that survival for years is possible. With continued advancement in knowledge pertaining to prevention and therapy, the outlook for the future may be distinctly more hopeful.

J. Prevention: 1. General measures: An effort should be made to avoid factors which may have etiological significance, particularly in known susceptible persons, including patients with coronary heart disease and especially those with complete heart block. For example, one should avoid, whenever possible, the administration of drugs by the intravenous route, and care should be taken to prevent the employment of toxic doses of drugs, especially digitalis and quinidine. An attempt should be made to prevent toxic concentrations of digitalis due to excessive mercurial-induced diuresis. DiPalma and Schults [16] reminded that in poisoning with drugs, such as digitalis and quinidine, conduction defects are the warning sign that fibrillation may begin.

2. Prevention of arrhythmias: Quinidine has commonly been used in persons with recent myocardial infarction, particularly if premature beats were noted, in an effort to prevent the development of ventricular tachycardia and subsequent ventricular fibrillation. Many feel that this practice is not justified. DiPalma and Schults,[16] for example, indicated that the use of quinidine as prophylaxis against ventricular fibrillation in myocardial infarction, even in the presence of extrasystoles, is not entirely rational and that there is little clinical or experimental evidence to justify it. Goodman and Gilman [25] stated that quinidine is a toxic drug and may in itself produce fibrillation, so that it should not be used for prophylactic purposes in patients with fresh myocardial damage. Rakov [26] warned that, since disease of bundle tissues may be impossible to detect, prophylactic administration of quinidine following coronary arterial occlusion always is potentially hazardous. Smith and co-workers [26] indicated that quinidine sulfate is of little use in the preventive treatment of the disordered mechanism caused by experimental occlusion in coronary arteries and that indeed it may hasten the onset of such mechanisms.

Some authors have suggested the use of digitalis for the prevention of arrhythmias. Scherf and Boyd [22] stated that if heart block is present digitalis may be of value in prevention of arrhythmias. Wégria [18] indicated that the reluctance to digitalize the patient with coronary occlusion and myocardial failure (on the grounds of increasing the risk of ventricular fibrillation) may be unwarranted if toxic doses of the drug are avoided. However, in the presence of derangement of intraventricular conductivity, Robinson and Bredeck [28] pointed out that the use of such drugs as chloroform, epinephrine, and strophanthin, which predispose the heart to ventricular fibrillation, is contraindicated. Newer drugs, including procaine amide, may prove to be of definite value not only in treatment but in prevention of arrhythmias.[15]

3. Treatment of ventricular tachycardia: This arrhythmia has usually been regarded as forerunner of ventricular fibrillation. Its treatment, usually with

25. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 547.

26. Smith, F. H.; McEachern, C. G., and Hall, G. E.: The Effect of Intravenous Administration of Quinidine Sulfate on the Development of Ventricular Fibrillation Following Sudden Occlusion of the Circumflex Branch of the Left Coronary Artery: Experimental Study, Am. Heart J. **20**:620-626 (Nov.) 1940.

quinidine, therefore, has been considered urgent. Fahr [27] stated that it is necessary to give quinidine to stop the ventricular tachycardia and prevent ventricular fibrillation. For this purpose, he has given up to 85 grains (5.5 gm.) in 24 hours. Armbrust and Levine [28] suggested that, although much has been said and written about toxic effects of quinidine in the treatment of ventricular tachycardia, these matters are of little importance, as the condition is already critical and often fatal if uncontrolled. According to DiPalma and Schults,[16] if ventricular tachycardia develops in a patient with previous bundle branch block, no contraindication to quinidine therapy is recognized. However, they advised caution and close observation. Kerr in discussion on the paper by Fahr,[27] however, warned that:

> If all patients with ventricular tachycardia are given quinidine there will be real trouble because a high percentage of these patients have serious vascular disease of the heart (with) block in the conduction system and since quinidine acts on the conduction system, tending to increase the block, as well as on the muscle . . . the dangers of . . . producing a ventricular fibrillation are considerable.

Enselberg and colleagues [29] stated that potassium is preferable to quinidine in treatment of the average patient with ventricular tachycardia. The potassium may be administered as potassium chloride, 2 to 10 gm. as 20% solution in citric acid syrup. Procaine amide has been used with considerable promise in the treatment of ventricular tachycardia. Feil and Rossman [2b'] concluded that procaine hydrochloride as a local anesthetic applied to the surface of the heart during cardiac operations may be of some use in preventing prefibrillary arrhythmias, but the effectiveness of quinidine could not, in their experience, conclusively be demonstrated.

K. Treatment: 1. General measures: The rational treatment of Adams-Stokes seizures depends upon the recognition of the underlying mechanism and the state of the intraventricular conduction. When these attacks are due to ventricular standstill, certain drugs, including epinephrine, ephedrine, and barium chloride, may be helpful. However, these drugs are usually contraindicated when the underlying mechanism is ventricular fibrillation. When defective intraventricular conduction is present in patients with seizures due to ventricular fibrillation, quinidine should not be used, or if it is used, the patient should be kept under close observation so that administration can be discontinued if aggravation results. Various drugs have been employed in the treatment of these seizures due to ventricular fibrillation with inconclusive and varying results. The drugs most commonly used have been those of the quinidine and digitalis groups, ephedrine, epinephrine, and various miscellaneous agents. We have been interested in the use of quinidine, especially in view of the results obtained in our case.

2. Quinidine: It is generally recognized that quinidine should be given intravenously only when the patient is unable to take the medicine orally. This is

27. Fahr, G.: Treatment of Cardiac Irregularities, J. A. M. A. **111**:2268-2275 (Dec. 17) 1938.

28. Armbrust, C. A., Jr., and Levine, S. A.: Paroxysmal Ventricular Tachycardia: Study of 107 Cases, Circulation **1**:28-40 (Jan.) 1950.

29. Enselberg, C. D.; Simmons, H. G., and Mintz, A. A.: The Effects of Potassium upon the Heart with Special Reference to Possibility of Treatment of Toxic Arrhythmias Due to Digitalis, Am. Heart J. **39**:713-728 (May) 1950.

emphasized by the fact that several fatalities have been reported as following its use intravenously. Quinidine lactate, which is now available commercially for intramuscular use, has been found to be relatively painless and no more toxic than when given orally in similar dosage.[30] Maximal cardiac effect is noted in 30 minutes, with peak effect lasting 2 to 6 hours and a small but significant effect persisting as long as 24 hours.

Several authors have reported favorable whereas others have noted unfavorable results with the use of quinidine.

(*a*) Favorable results. Among those who have reported favorably on the use of quinidine in ventricular fibrillation, the following authors are cited: Friedberg [31] recommended quinidine in increasing doses until there is definite toxicity or the attacks are controlled. Stewart [32] maintained that quinidine may prevent attacks, even though massive doses may induce them. Dock [2j] prevented attacks in his patients with transient ventricular fibrillation but an otherwise normal heart. Fahr [27] suggested the administration of quinidine in sufficient dosage to stop ventricular fibrillation. Levine and Harvey [23] stated that quinidine may be helpful in decreasing the frequency of the attacks. Brams [33] held quinidine to be the drug of choice and suggested its administration as in paroxysmal ventricular tachycardia. Katz [21] reported its use in one patient with apparently good effect. Wiggers and co-workers [18] experimentally indicated that quinidine raises the fibrillation threshold but warned that too large doses may produce ventricular fibrillation. Scherf and Boyd [22] stated that if heart block is absent quinidine may be given between attacks to prevent recurrences. In the case reported by Escamilla,[2q] the benefit from quinidine was considered to be questionable.

(*b*) Unfavorable results. On the other hand, the possibility of adverse effects is stressed by many authors. Cahall [2r] suggested that the use of quinidine in ventricular fibrillation is contraindicated if complete heart block is present. Grollman [34] held that the use of quinidine is contraindicated in heart block. Stewart [35] concluded that quinidine is contraindicated in complete heart block and in bundle branch block. Kerr and Bender [2b] maintained that quinidine may in certain circumstances induce fibrillation. Fahr [27] stated that when there exists a block in the conduction system quinidine, by increasing the block, may produce ventricular fibrillation. One of Beckwith's [36] patients with bundle branch block may have had Adams-Stokes seizures due to paroxysmal ventricular fibrillation following administration of quinidine

30. Blinder, H.; Burstein, J.; Horowitz, W.; Gersh, E., and Snellin, R.: Studies on the Effects of Parenteral Quinidine Administration, Arch. Int. Med. **86**:917-933 (Dec.) 1950.

31. Friedberg, C. K.: Disease of the Heart, Philadelphia, W. B. Saunders Company, 1949, p. 287.

32. Stewart, H. J.: Functional Disorders of Heart, in Textbook of Medicine, edited by R. L. F. Cecil and others, Ed. 7, Philadelphia, W. B. Saunders Company, 1947, p. 1266.

33. Brams, W. A.: Treatment of Heart Disease, Philadelphia, W. B. Saunders Company, 1948, p. 105.

34. Grollman, A.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1951, p. 367.

35. Stewart, H. J.: Management of Disorders of Cardiac Rhythm, Am. J. Med. **5**:110-126 (July) 1948.

36. Beckwith, J. R.: Adams-Stokes Syndrome as a Complication of Myocardial Infarction: Report of 3 Cases Demonstrating 2 Different Underlying Mechanisms, Virginia M. Monthly **70**:336-342 (July) 1943.

for ventricular tachycardia complicating acute myocardial infarction. Rakov [2f] stated that in patients with disease of the bundle tissues quinidine may incite and perpetuate ventricular fibrillation. Gold [2q] found no apparent benefit in one case. According to Scherf and Boyd,[22] quinidine should not be given in heart block, since it may favor the appearance of ventricular fibrillation. Davis and Sprague [2k] indicated that quinidine had an unfavorable effect in their case. Sigler [11] noted that quinidine brought on attacks in one of his patients with greater frequency. DiPalma and Schults [16] stated that in cases of complete heart block, bundle branch block, or intraventricular conduction defect, quinidine may precipitate ventricular tachycardia and ventricular fibrillation. In this connection, DiPalma and Schults [16] wrote as follows:

> The problem of when not to use quinidine is to our mind more important than indications for its use. We are chagrined to find several authoritative articles and most text books completely fail to mention the very grave hazard of quinidine therapy when complete heart block, bundle branch block or intraventricular conduction defects are present. Fatalities from quinidine therapy result most often in these cases and, although not reported, we feel that this is true. This viewpoint is not only substantiated by knowledge of the physiology of antifibrillatory drugs discussed in the previous section but by clinical experience. In the past year we have been able to collect ten cases of severe quinidine myocardial toxicity occurring when quinidine or quinidine-like drugs were administered in the presence of conduction defects. . . . During the same period of time quinidine was administered to scores of cases with arrhythmias and various types of heart disease, but without conduction defects, in which quinidine myocardial toxicity did not become evident. . . . This does not mean that quinidine is absolutely contraindicated in bundle branch block but its use must be attended with great caution.

3. Epinephrine effect: With reference to the use of the epinephrine-ephedrine group of drugs, some authors, including Fahr, Parkinson, Levine, Matthew, Cahall, and Sigler, have noted favorable results. However, Schwartz and Jezer [37] stated that use of these drugs is distinctly contraindicated in Adams-Stokes seizures due to ventricular fibrillation, and their indiscriminate administration in such patients may result in death. Brams [33] stated that epinephrine and digitalis are contraindicated in paroxysmal ventricular fibrillation. With reference to the use of digitalis, Scherf and Boyd [22] reported that if heart block is present, especially complete heart block, digitalis should be administered, since often it prevents the appearance of tachycardia. DiPalma and Schults,[16] however, stated that in large doses digitalis may produce ventricular tachycardia and fibrillation. Digitalis may convert ventricular tachycardia to ventricular fibrillation.

4. Miscellaneous: According to Stewart,[35] sedatives, such as bromides or phenobarbital, seem to be helpful in patients in whom convulsions occur as a result of ventricular fibrillation. Digitalis and ephedrine help in ventricular standstill but aggravate ventricular fibrillation. Sigler [11] reported favorably upon the use of hypertonic dextrose solution intravenously, 50 cc. of 50% solution. However, he stated that in his experience of four cases dextrose therapy was more valuable when the seizures were due to ventricular standstill than when they were due to ventricular fibrillation. Wiggers [13] found that papaverine experimentally raises the fibrillary threshold, but rapid or large doses may induce ventricular fibrillation. DiPalma and

37. Schwartz and Jezer.[2r] Schwartz, S. P., and Jezer, A.: The Action of Adrenalin on Patients with Complete Heart Block and Stokes-Adams Seizures, Am. Heart J. **7**:652-667 (June) 1932.

Schults [16] concluded that papaverine can hardly be considered a safe drug in the dosage necessary to stop ventricular fibrillation. Katz [21] used papaverine with quinidine in one case with apparently good effect.

Zwillinger [38] used magnesium sulfate with good effect, the paroxysms being abolished by intracardiac and intravenous injections of this drug.

Enselberg and co-workers [28] suggested potassium or procaine amide, especially in the prefibrillary state. DiPalma and Schults,[16] however, warned that procaine can be given intravenously in only relatively small doses, since it is a marked cardiac and respiratory depressant.

The use of coronary vasodilators and oxygen, as suggested by Friedberg,[31] may be of value, since, as Wiggers [13] has shown experimentally, induced ischemia causes decrease in the fibrillary threshold.

Schwartz and Jezer [39] indicated that barium chloride is contraindicated in Adams-Stokes seizures due to ventricular fibrillation.

In instances of ventricular fibrillation occurring at operation, Beck and associates [20] described a method of Hooker, Wiggers, and Beck in which 5 cc. of 1% procaine hydrochloride was injected into the right ventricle and 5 cc. applied to the surface of the heart, followed by a period of cardiac massage. The heart was then placed between two large electrodes and ordinary 110-volt alternating current with 1.5 amp. was momentarily impressed through the heart and repeated as necessary. Massage again was instituted until the vigor of the beats was sufficient for circulation. In some instances in which the fibrillation changed to asystole, epinephrine (0.5 cc. of 1 : 1,000 solution diluted to 5 cc. in isotonic sodium chloride solution) has been injected into the right ventricle. In 1947 these authors reported the first recovery in a patient after 35 minutes of ventricular fibrillation with no detectable neurologic or cardiac damage.

DiPalma and Schults [16] indicated that antihistaminics are being investigated and that preliminary studies have suggested possible usefulness.

SUMMARY AND CONCLUSIONS

Summary.—A case is described of paroxysmal ventricular fibrillation producing Adams-Stokes seizures which illustrates the following: (*a*) the importance of establishing the underlying mechanism of Adams-Stokes attacks; (*b*) the association of ventricular standstill with ventricular fibrillation in the production of Adams-Stokes attacks; (*c*) the potential aggravating effect of quinidine in ventricular fibrillation, especially in the presence of complete heart block and intraventricular block.

The 51 reported cases of paroxysmal ventricular fibrillation producing Adams-Stokes attacks are outlined and analyzed.

The literature is surveyed, and present concepts concerning the definition, clinical pattern, incidence, etiology, pathology, prevention, and treatment of paroxysmal ventricular fibrillation are reviewed.

Conclusions.—Definition: Two types of paroxysmal rapid heart action producing Adams-Stokes seizures, namely, prefibrillary ventricular tachycardia ("ven-

38. Zwillinger, L.: Über die Magnesiumwirkung auf das Herz, Klin. Wchnschr. **14**:1429-1433 (Oct. 5) 1935.

39. Schwartz, S. P., and Jezer, A.: Stokes-Adams Syndrome: Some Clinical and Graphic Observations on Cardiac Mechanism Underlying Syncopal Seizures, M. Clin. North America **17**:213-231 (July) 1933.

tricular flutter") and ventricular fibrillation, are closely related clinically and are considered to represent essentially the same fundamental mechanism.

Clinical Pattern: The severity of symptoms varies with the degree of interference with the cerebral circulation, as related to duration of the ventricular fibrillation. Thus, the severity may range from mild transient dizziness and visual disturbances with "black-out" to severe convulsive episodes and death.

Incidence: Paroxysmal ventricular fibrillation occurs more commonly as a cause of syncope and Adams-Stokes attacks than has been recognized generally.

Diagnosis: Consideration always should be given to the possibility of prefibrillary ventricular tachycardia as a cause of syncope or Adams-Stokes attacks. An electrocardiogram should be made if possible during an attack, but interval studies may also be valuable in suggesting the diagnosis.

Prognosis: Though always serious, the prognosis, with proper management, definitely may be increasingly more hopeful.

Etiology: Paroxysmal ventricular fibrillation occurs most frequently in persons with serious heart disease, chiefly with atrioventricular dissociation and after coronary occlusion with myocardial infarction. However, it has been reported in several instances in persons with no demonstrable heart disease. Factors favoring ventricular fibrillation include anoxia, ischemia, intravenous administration of drugs, and toxic doses of drugs, especially digitalis and quinidine. Ventricular fibrillation also may occur in chloroform or cyclopropane anesthesia, especially when the circulating epinephrine concentration is increased by injection or anxiety.

Prevention: The following measures may prove helpful in the prevention of ventricular fibrillation: (*a*) avoidance whenever possible of intravenous administration of medicaments, particularly in patients known to have cardiac disease; (*b*) avoidance of toxic doses of drugs, especially digitalis and quinidine; (*c*) observance of the important contraindications to the use of quinidine in patients with complete heart block or intraventricular block; (*d*) prevention of frequent premature ventricular contractions, especially in patients with recent myocardial infarction by use of procaine amide ("pronestyl") or, in the absence of conduction defects, by the cautious use of quinidine; (*e*) treatment of ventricular tachycardia by use of procaine amide or, in the absence of conduction defects, by the cautious use of quinidine.

Treatment: Since, to date, there is no standard therapeutic program for the management of ventricular fibrillation, the treatment must be individualized. Drugs useful in the treatment of Adams-Stokes seizures due to ventricular standstill (including epinephrine, ephedrine, and barium chloride) probably should not be used. Among the measures which may be given consideration are the following: (*a*) oxygen therapy; (*b*) cautious administration of coronary vasodilators, such as aminophyllin and papaverine; (*c*) administration of procaine amide orally or cautiously intravenously; (*d*) administration of sedatives, including bromides and phenobarbital; (*e*) hypertonic dextrose infusions; (*f*) potassium chloride administration; (*g*) cautious administration of magnesium sulfate intravenously; (*h*) in special instances, electrical stimulation with massage.

Quinidine, in most instances, probably should not be used, particularly in the presence of intraventricular or complete heart block.

GENETIC STUDIES ON CORONARY ATHEROSCLEROSIS DEVELOPING AFTER THE AGE OF SIXTY YEARS

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EVIDENCE has accumulated that an error of lipid metabolism is closely related to the process of atherogenesis in man and experimental animals.[1] Many attempts have been made to characterize this disturbance of lipid metabolism. Elevation of the serum cholesterol level,[2] alteration of the cholesterol-phospholipid ratio,[1f-h] higher concentrations of giant lipoprotein molecules,[1i,j] and abnormal shifts from alpha to beta lipoprotein [1m] have been studied. The precise role of each of these factors is still under investigation; each represents a different facet of the faulty lipid metabolism.

Our previous studies on patients with coronary artery disease whose symptoms began before the age of 50, as well as on their siblings,[3] and on families with xanthomatosis [4] led to the conclusion that the common factor for patients with coronary atherosclerosis may be a genetically transmitted fault of lipid metabolism manifesting itself as hypercholesteremia.[4] Familial xanthomatosis is the severest form of this inherited disturbance. Many patients with coronary artery disease

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1. (*a*) Anitschkow, N., in Arteriosclerosis: A Survey of the Problem, edited by E. V. Cowdry, New York, The Macmillan Company, 1933, Chap. 10. (*b*) Katz, L. N., and Dauber, D. V.: Pathogenesis of Atherosclerosis, J. Mt. Sinai Hosp. **12**:382, 1945. (*c*) Hueper, W. C.: Arteriosclerosis, Arch. Path. **39**:187, 1945. (*d*) Gubner, L., and Ungerleider, H. E.: Arteriosclerosis: A Statement of the Problem, Am. J. Med. **6**:60, 1949. (*e*) Steiner, A., and Domanski, B.: Serum Cholesterol Level in Coronary Arteriosclerosis, Arch. Int. Med. **71**:397, 1943. (*f*) Kellner, A.; Correll, J. W., and Ladd, A. T.: The Influence of Intravenously Administered Surface-Active Agents on the Development of Experimental Atherosclerosis in Rabbits, J. Exper. Med. **93**:385, 1951. (*g*) Gertler, M. M.; Garn, S. M., and Bland, E. F.: Age, Serum Cholesterol and Coronary Artery Disease, Circulation **2**:517, 1950. (*h*) Gertler, M. M., and Garn, S. M.: Lipid Interrelationship in Health and in Coronary Artery Disease, Science **112**:14, 1950. (*i*) Gofman, J. W.; Lidgren, F.; Elliot, H.; Mantz, W.; Hewitt, J.; Strisower, B., and Herring, V.: The Role of Lipids and Lipoproteins in Atherosclerosis, ibid. **111**:167, 1950. (*j*) Gofman, J. W., and others: Blood Lipids and Human Atherosclerosis, Circulation **2**:161, 1950. (*k*) Keys, A.: Cholesterol, Giant Molecules and Atherosclerosis, J. A. M. A. **147**:1514, 1951. (*l*) Dock, W.: The Causes of Arteriosclerosis, Bull. New York Acad. Med. **26**:182, 1950. (*m*) Barr, D. P.; Russ, E. M., and Eder, H. A.: Protein Lipid Relationship in Human Plasma: I. In Normal Individuals; II. In Atherosclerosis and Related Conditions, Am. J. Med. **11**:468, 1951.

2. Footnote 1*b* to *e*, *g*, and *h*.

3. Boas, E. P.; Parets, A. D., and Adlersberg, D.: Hereditary Disturbance of Cholesterol Metabolism: A Factor in the Genesis of Atherosclerosis, Am. Heart J. **35**:611, 1948.

4. Adlersberg, D.; Parets, A. D., and Boas, E. P.: Genetics of Atherosclerosis, J. A. M. A. **141**:246, 1949.

are affected with a milder form of disturbed lipid metabolism. Derangement of lipid metabolism resulting in hypercholesteremia may explain the familial incidence of coronary artery disease.

In continuation of these studies, observations on 100 patients whose clinical evidences of coronary artery disease appeared after the age of 60 have been completed.

PLAN OF STUDY

The patients of this group represented consecutive patients with proved coronary artery disease seen in the office practice of one of us (E. P. B.), unselected except for their age and the exclusion of diabetics. There were 94 men and 6 women. The average age at onset of symptoms was 63.4 ± 3.5 years; at the time of examination, 65.8 ± 4.4 years. The youngest patient was 60 years old, the oldest 82. The great majority of the patients were of Jewish origin.

The Schoenheimer-Sperry method was employed for the determination of the total and esterified serum cholesterol. In our experience, the determination of total serum cholesterol by the Schoenheimer-Sperry method gives results which are approximately 5% lower than those obtained by the Bloor method; in the higher ranges (over 280 mg. per 100 ml.) this difference may be considerably greater. On the basis of previous studies we have regarded a serum cholesterol reading of 300 mg. or more per 100 ml. by the Bloor method and of 280 mg. or more per 100 ml. by the Schoenheimer-Sperry method as hypercholesteremia.

RESULTS

The values of total serum cholesterol ranged in this group of 100 patients from 185 to 371 mg. per 100 ml.; the average was 279 ± 4.67 mg. (standard difference of the means). The esterified serum cholesterol averaged 205 mg. per 100 ml. and thus represented 73% of the total serum cholesterol. Forty-three, or 43%, of the patients, exhibited hypercholesteremia. This corresponds with the results of the study by Morrison and associates [5] in which 48% of patients with coronary arteriosclerosis over the age of 60 had serum cholesterol readings above 260 mg. per 100 ml.

The previous series included 122 patients with coronary artery disease whose symptoms began before the age of 50 years.[3] The average age at onset was 42 years; at examination, 45 years. Cholesterol determinations in the serum were made by the Bloor method. The average serum cholesterol was 316 ± 7.49 mg. ($S.D._M$) per 100 ml. The individual readings ranged from 199 to 845 mg. per 100 ml. and were above 300 mg. in 58%. The families of 50 patients were available for study. In one-third of these families all or most of the siblings had serum cholesterol levels of more than 300 mg. per 100 ml. and in nine additional families one-half of the siblings had hypercholesteremia.

It is significant that in the present series of older patients whose average age was 65.8 years, the average level of serum cholesterol was lower than in those whose symptoms of coronary artery disease had started before the age of 50 (average age, 45 years) and that fewer among them had hypercholesteremia. In normal men the mean serum cholesterol level is practically identical at ages 45 and 65.[6]

5. Morrison, L. M.; Hall, L., and Chaney, A. L.: Cholesterol Metabolism: Blood Serum Cholesterol and Ester Levels in 200 Cases of Acute Coronary Thrombosis, Am. J. M. Sc. **216**:32, 1948.

6. (*a*) Keys, A., and others: The Concentration of Cholesterol in the Blood Serum of Normal Man and Its Relation to Age, J. Clin. Invest. **29**:1347, 1950. (*b*) Kornerup, V.: Concentrations of Cholesterol, Total Fat and Phospholipid in Serum of Normal Man: Report of Study with Special Reference to Sex, Age and Constitutional Type, Arch. Int. Med. **85**:398, 1950.

Of the 94 men, 42 had hypertension. Of these, 19 had elevated and 23 normal serum cholesterol figures.

Forty-eight of 86 men on whom data are available had a corneal arcus. An arcus was present in 51.5% of those aged 60 to 69 and in 72.2% of those over the age of 70. The corneal arcus appears with increasing frequency in normal persons with advancing years. Between the ages of 60 and 69 about 37% and from ages 70 to 79 about 73% of men have a corneal arcus.[7] In the present series the presence or absence of an arcus bore no relation to the level of plasma cholesterol. Only 1 patient had xanthelasmas, and 1 had tendon xanthomas, in contrast to 11 with xanthelasmas and 3 with xanthomatosis in the series of 122 younger patients with coronary artery disease.

FAMILIAL STUDIES

Familial studies of older persons are very difficult because at this age siblings are widely scattered and many are dead. Under these conditions we were able to examine one or more siblings in only 28 families (Table 1). In one family five sibs, in two families three sibs, and in nine families two sibs were hypercholesteremic; as may be seen from Table 1, many sibs were not available for examination.

There were 127 siblings in the 28 families that were studied. Cholesterol determinations were made in 52 of these, or 41%. Twenty-five, or 48%, of those examined showed serum cholesterol levels over 280 mg. per 100 ml. i. e., they had hypercholesteremia. Thirteen of the siblings whose serum cholesterol was not determined had heart disease.

The frequency distribution of serum cholesterol levels of 52 siblings examined in the 28 families of the present series, as well as the distribution of the index patients, is presented in the Figure. The frequency distribution of serum cholesterol levels of the index patients and of their siblings show a striking parallelism. In view of the relation that exists between age and serum cholesterol,[6] the serum cholesterol levels of the siblings have been arranged in relation to age. For siblings in the age groups 41 to 50 and 51 to 60 the average serum cholesterol was 287 mg. per 100 ml., while those in the age group 61 to 70 had an average of 258 mg. per 100 ml. Thus, the trend found in normal persons is also evident in the siblings, although on a higher level.

Table 2 presents a comparison of the present series with the previous group in which the index patients exhibited coronary artery disease before the age of 50. In the younger group there were 145 siblings, and serum cholesterol determinations were made in 113, or 78%. Thirty-six, or 32%, of those examined had hypercholesteremia.

Among the brothers and sisters of the index patients over the age of 60, there were 18, or 14.5%, who had coronary artery disease; among the siblings of the index patients under 50 years of age, 12, or 8.3%, had coronary artery disease. This difference is to be expected since the siblings of the older group themselves were older and so had more opportunity to acquire atherosclerotic coronary artery disease.

Studies of complete families in this age group are very difficult to obtain. We were fortunate in being able to study two families in greater detail. These two

7. Boas, E. P.: Treatment of the Patient Past 50, Ed. 3, Chicago, The Year Book Publishers, Inc., 1947, p. 427.

TABLE 1.—*Total Serum Cholesterol and Esterified Cholesterol Levels Among Siblings (and Children) of Patients with Coronary Atherosclerosis, Over Sixty Years of Age, Including Data on Longevity of Parents in Twenty Families*

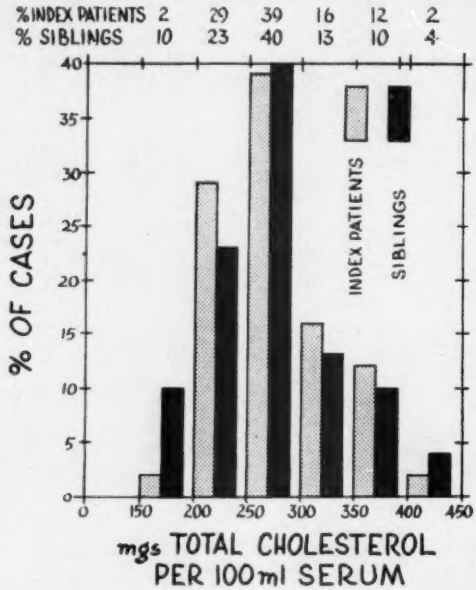
Index Patient			Parents		Siblings*								
Patient No.	Sex; Age	Serum Cholesterol/ Cholesterol Esters, Mg./100 Ml.	Father	Mother	1	2	3	4	5	6	7	8	Comment
1	M; 67	370/276	?	D 73	S; 70; ?	B; 64; 341/253	B; 61; ?; Hy	B; 59; 266/197; Hy, Co	S; 56; 291	S; 54; dead	B; 51; 295	B; 47; 301; Hy	Sib 6 died of Hodgkin's disease; father died in young age of pneumonia
2	M; 72	205/139	D 85	D 85	B; 70; 247/206	B; 68; ?; CA	B; 65; dead; Co	S; 61; 277	B; 60; 293; Co	B; 57; 293	B; 55; 284	S; 52; 269	.....
3	M; 63	243/179	D 71	D 81	B; 55; 290/208	S; 50; 351/269	S; 50; 351/269	B; 48; 238/138	B; ?	B; ?	S; ?	S; ?	.....
4	M; 62	256/187	D 62	D 59 Co	B; 55; ?; Hy	S; 49; ?	S; 48; 297/234; Hy	B; 48; ?	B; dead	B; dead	S; dead	S; dead	Sibs 5, 6, 7, 8 killed in war
5	M; 74	347	....	....	S; 52; 442/328	B; dead; Co	B; dead	B; ?	B; ?	S; ?; Co	S; ?; Co, Hy	.....	Wife, aged 72, 343/245, Co; Sn, aged 50, 314/235, Co; Sn, aged 48, 305/223; Sn, aged 44, 384/274
6	M; 64	321/237	....	....	S; 58; 426/313	S; 52; 372/269	B; dead	B; dead	B; dead	B; dead	.....	.....	Sibs 3, 4, 5, 6 killed in war
7	M; 76	215/167	....	....	S; 78; ?	S; 74; dead	B; 73; ?	B; 67; 191/134	S; 50; dead	S; 50; dead	.....	.....	Sib 4 died of cancer
8	M; 70	238	....	....	B; 60; 196/141; Hy	S; 58; 394/292	S; 55; 270/199	B; dead	B; dead	.....	.....	.....	Sib 4 died of pneumonia; sib 5 of asthma
9	M; 64	291/213	D 77	L 89	B; 67; ?	B; 63; ?	S; 57; 366; Hy	S; 51; 246	B; 50; ?; Hy	.....	.....	.....	Father died of carcinoma
10	M; 66	255/191	D 85	D 30	S; 65; 242/180	B; 62; ?	B; 58; dead; Co	B; 56; 250/184	B; 54; dead	.....	.....	.....	Mother died at childbirth, aged 30; sib 5 died suddenly, had diabetes
11	M; 68	238	D 89	D 64	B; 63; 155/126	B; 60; ?	B; 56; 192/154	S; ?	S; ?	.....	.....	.....	Mother died of influenza
12	M; 61	368/294	D 75	D 52	B; 64; 229/173	S; ?	S; ?	S; ?	S; 50; dead	.....	.....	.....	Sibs 2, 3, 4 are well and live out of town; sib 5 died of leukemia
13	M; 65	275/204	....	....	B; 59; 319	S; ?	S; ?	S; ?	B; dead	.....	.....	.....	Sib 5 died of carcinoma
14	M; 61	275/207	D 60	D 88	B; 57; 257/188	S; dead	B; ?	B; ?	B; ?	.....	.....	.....	Sib 2 died in infancy; sibs 3, 4, 5 reside abroad

15	M; 64	215/190	....	....	B; 70; dead	S; 65; dead	S; 59; 265/194	S; 56; ?	S; dead; Co	.....	.....	.....	Sib 1 died suddenly; sib 2 had diabetes; sib 5 killed in war
16	M; 67	350/250	D 56	D 77	B; 62; 350/250; Hy	S; 62; dead	B; 57; dead; Co	B; ?	.....	.....	.....	.....	Sib 2 had diabetes; Father died of carcinoma
17	M; 70	205/151	D 78	D 67	B; 63; dead	B; 62; 331/247	B; 60; dead; Co	B; dead	.....	.....	.....	.....	Mother died of carcinoma; sib 1 died of carcinoma; sib 4 died of typhus
18	M; 68	265/199	D 49	D 53	B; 62; 282/215	S; 58; 258/183; Co	S; 55; 314/233	.....	.....	.....	.....	.....	.....
19	F; 66	299/219	....	....	B; 70; 265/198	B; 64; 209/148; Co	B; 55; 244/184	.....	.....	.....	.....	.....	.....
20	M; 64	238/168	D 72	D 66	B; 63; ?; Co	S; 59; 309/213; Co	B; 52; 242/184	.....	.....	.....	.....	.....	.....
21	M; 67	297/203	D 80	D 40	B; 68; 297/214	B; 66; ?	S; dead	.....	.....	.....	.....	.....	Mother died after operation following an accident; sib 3 died in infancy
22	M; 60	379	L 94	D 67	S; 56; 277	B; dead	B; dead	.....	.....	.....	.....	.....	Sibs 2 and 3 died in infancy
23	M; 62	249/178	D 70	D 70	B; 65; dead	B; dead	B; 59; 225/168	.....	.....	.....	.....	.....	Sib 1 died of carcinoma; sib 2 of diabetes
24	M; 73	186/135	D 84	D 60	B; 69; 195	B; 60; ?	B; 53; 225/175	.....	.....	.....	.....	.....	.....
25	M; 60	299/205	D 60	D 60	B; 48; 299/222	B; 44; 235/161	.....	.....	.....	.....	.....	.....	Father died of carcinoma; mother of grippe
26	M; 60	273/204	....	....	B; 66; ?; Co	S; 55; 319	.....	.....	.....	.....	.....	.....	.....
27	M; 63	272/210	D 60	L 85	B; 63; 235/204; Co	S; 57; dead; Hy, Co	.....	.....	.....	.....	.....	.....	.....
28	M; 67	369	D 68	D 73	B; 65; ?	B; ?	.....	.....	.....	.....	.....	.....	Father died of carcinoma; mother died of hypertension; wife, aged 60, 518/397; D, aged 47, 354/253; Sn, aged 44, 319; D, aged 33, 336

* Siblings and children are arranged according to age and are living and well unless otherwise noted. B, brother, S, sister, Sn, son, D, daughter, indicate relationship to index patient. First number indicates age and the second and third total and esterified serum cholesterol values expressed in milligrams per 100 ml. Hy is hypertensive cardiovascular disease; Co, coronary artery disease; CA, cerebral accident; D, died (number indicates age at death), and L, living (number indicates age).

families are briefly presented as an illustration of the hereditary tendencies that may be manifest in older patients with coronary artery disease.

J. W., a white man, first had symptoms of angina pectoris at the age of 65. He had no hypertension, and his electrocardiogram was normal. One year later, he experienced a coronary occlusion. He did well, although his anginal pain on effort persisted. At the age of 72 intermittent claudication developed. He died at 74 years of age from another coronary occlusion. His serum cholesterol at the age of 74 was 347 mg. per 100 ml. One sister, who was examined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mgs TOTAL CHOLESTEROL PER 100 ml SERUM

Distribution of total serum cholesterol values among 100 index patients more than 60 years of age with proved coronary atherosclerosis and 52 siblings.

TABLE 2.—*Comparison of First and Second Series*

Series*	Probands	No. of Families Studied	% of Families Studied	Total of Sibs	No. Examined	Normocholesteremic Sibs		Hypercholesteremic Sibs	
						No.	%†	No.	%†
1	122	50	41	145	118	77	68	36	32
2	100	28	28	127	52	27	52	25	48

* First series composed of patients with coronary artery disease under the age of 50. Second series were patients with coronary artery disease over the age of 60.
† Percentage of those examined.

at the age of 52, was apparently well but had a serum cholesterol of 442 mg. and cholesterol esters of 338 mg. per 100 ml. One brother had died of coronary disease. Two sisters had heart disease. Two brothers were reported to be well. J. W.'s wife, aged 72 when examined, had no symptoms but had physical signs of calcareous aortic stenosis and an abnormal electrocardiogram. Her serum cholesterol was 343 mg. and cholesterol esters were 245 mg. per 100 ml. One son experienced a coronary occlusion at the age of 46. His serum cholesterol determined when he was aged 50 was 314 mg. and cholesterol esters were 233 mg. per 100 ml. Two other sons, aged 44 and 48, were clinically well and had serum cholesterol values of 384 and 305 mg. and cholesterol ester levels of 274 and 223 mg. per 100 ml., respectively.

J. Z., a white man, experienced myocardial infarction at the age of 60. He had no hypertension. The electrocardiogram showed typical posterior wall infarction. He did well but had angina pectoris on effort. He experienced anginal pain on walking two blocks. His electrocardiogram remained unchanged; his blood pressure rose to 165/100; serum cholesterol was 351 mg., and cholesterol esters were 271 mg. per 100 ml. He had two living brothers who were well. His wife, examined at the age of 68, had angina pectoris, a normal electrocardiogram, a serum cholesterol value of 518 mg., and cholesterol ester of 397 mg. per 100 ml. One son, aged 44, and a daughter, aged 33, had serum cholesterol levels of 319 mg. and 336 mg. per 100 ml., respectively, and another daughter, aged 47, had a serum cholesterol value of 354 mg. and a cholesterol ester level of 253 mg. per 100 ml. All children were examined and found well.

The age at death of the parents of 26 of our index patients was obtainable, while it was unknown in 74. Fourteen fathers died when more than 60 years of age; most of them when more than 70. Ten fathers and three mothers died before age 50; pneumonia and tuberculosis accounted for most of these deaths. Although the available data do not permit conclusions concerning longevity of the parents of the entire group, one can state that, in spite of the familial predisposition to atherosclerosis in this group, the longevity of the parents in the cases in which such data were known was not affected.

COMMENT

Keys and colleagues [6a] studied the relation between serum cholesterol levels and age. In persons within the age range of 17 to 30 years no differences were found between men and women as to averages, individual variability, and age trend. In men above the age of 30 there was an average increase per year of 2.2 mg. of total cholesterol per 100 ml. of serum up to the age of 60, with a decrease beyond this age.

The normal persons in whom serum cholesterol determinations were performed by Keys and his associates represented a portion "of the population in an upper Midwestern metropolitan area and were engaged in business, professional, and scholastic pursuits." The population group studied by us in the previous and present series consisted to a great extent of garment workers of Jewish descent. Thus, we are dealing with two groups of different ethnic, cultural, economic, and social backgrounds. Studies at this hospital have shown that in analogy with other inborn disturbances of lipid metabolism there is higher frequency of familial hypercholesteremia among the Jewish segment of the population in the New York area.[8] However, the variation of cholesterol level with age in both of our series runs parallel to that found by Keys and associates,[6a] and Kornerup.[6b]

The present study revealed that, although close to one-half of persons who displayed symptoms of coronary artery sclerosis after the age of 60 had hypercholesteremia, the incidence of the lipid metabolism disturbance was lower than in the younger group. However, the incidence of hypercholesteremia among the siblings of the older series was as high as, if not higher than, that among the siblings of the younger group.

Although the hereditary trends to hypercholesteremia seemed to be of the same order in old as in young persons with coronary artery disease, the intensity of the lipid metabolism disturbance was less marked in the older age group, as evidenced

8. Adlersberg, D.: Seminars on Arteriosclerosis: Hypercholesteremia with Predisposition to Atherosclerosis: An Inborn Error of Lipid Metabolism, Am. J. Med. **11**:600, 1951. Adlersberg, D.; Schaefer, L. E., and Drachman, S. R.: Incidence of Hereditary Hypercholesteremia, J. Lab. & Clin. Med. **39**:237, 1952.

by lower serum cholesterol levels, a much smaller incidence of xanthelasma and xanthoma, and probably a tendency to longevity among the parents. If it is true that hypercholesteremia in these patients, as a part of disturbed lipid metabolism, is a genetically determined abnormality, they must have had the predisposition from birth. Yet the manifestations of atherosclerosis were much delayed.

Familial xanthomatosis is the severest form of abnormal lipid metabolism, and coronary atherosclerosis is frequent in members of these families. Coronary artery disease in the young is an expression of a less pronounced derangement of lipid metabolism, and in the elderly, a result of the gradual and protracted effects of a still milder and more indolent metabolic disturbance. An analogy may be drawn with diabetes and hypertension, diseases which are severe and progressive in the young and mild in the aged. Anitschkow long ago emphasized the time factor and indicated that "the genesis of atherosclerosis depends not only on the intensity but also on the duration of the cholesterine congestion that is present in the organism."[1]

SUMMARY

A genetically transmitted disturbance of a lipid metabolism manifesting itself as hypercholesteremia appears to be a common denominator for certain groups of patients with coronary atherosclerosis. Familial xanthomatosis represents the severest form of faulty lipid metabolism, and many members of these families are affected with atherosclerosis of the coronary arteries.[4] Coronary artery disease in unselected young persons is an expression of a milder derangement of lipid metabolism.[3]

This study is concerned with a group of 100 unselected patients with coronary artery disease whose symptoms began after the age of 60 years. The average age at onset was 63.4 years, and the average age at time of study was 65.8. The average serum cholesterol level of these patients was 279 ± 4.67 mg. per 100 ml. (standard difference of the means) by the Schoenheimer-Sperry method. It was lower than in a previously studied group of patients whose symptoms of coronary artery disease had started before the age of 50.[4] Among the older group fewer were hypercholesteremic. This is significant because in normal men the mean serum cholesterol level is almost identical at ages 45 and 65 (235.5 mg. per 100 ml. at 45, and 236.7 mg. per 100 ml. at 65).[6a]

Familial studies of older patients are difficult, and only 28 families of the 100 probands could be partially examined. Of the 52 siblings studied, 25 (or 48%) showed serum cholesterol levels of more than 280 mg. per 100 ml. The frequency distribution of serum cholesterol levels of the probands and of their siblings showed a striking parallelism. The variation of serum cholesterol level with age was also seen in the sibs. This was evident, although the readings tended to be higher than those for normal persons.[6]

This study suggests that the derangement of lipid metabolism of patients whose coronary artery disease becomes manifest after the age of 60 represents a more indolent metabolic disturbance than that encountered in the younger patients affected with this disease. However, the incidence of hypercholesteremia among the sibs of the older group does not differ significantly from that among the sibs of the younger group.

Dr. L. C. Dunn, Professor of Zoology, Columbia University, and Dr. A. G. Steinberg, Children's Medical Center, Boston, aided in the analysis of the genetic aspects presented in this study.

ROLE OF THE CENTRAL NERVOUS SYSTEM IN METABOLISM OF ELECTROLYTES AND WATER

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AN INTEREST in the influence of the central nervous system on the metabolism and excretion of electrolytes and water dates back at least to the middle of the 19th century, when Bernard [1] observed a diuresis unrelated to glycosuria following puncture of a particular area of the floor of the fourth ventricle. His observation was confirmed and extended by Jungmann and Meyer.[2] Since that time a considerable body of data has accumulated concerning the manner in which special structures within the central nervous system respond to and participate in the control of the volume and tonicity of the body fluids. The interrelationships among these several influences are quite intimate and so ordered as to provide a series of automatic adjustments that allow a high degree of precision in the control of the several dimensions of body fluid in health and in disease.

The ingestion of those materials that comprise the constituents of body fluid is the first step in their metabolic history. It is well, therefore, to consider first the mechanisms that lead ultimately to the ingestion of an appropriate amount of the largest single constituent, water.

Thirst, which is the subjective sensory impression of an absolute or relative deficit of water (and, perhaps, specifically of volume), is the net result of several physiologic influences. Moreover, in man there are other influences related to social and psychologic conditioning which are difficult to analyze in any quantitative

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1. Bernard, C., cited by Cushny, A. R.: The Secretion of the Urine, London, Longmans, Green & Co., 1926, Chap. 7, p. 135.

2. Jungmann, P., and Meyer, E.: Experimentelle Untersuchungen über die Abhängigkeit der Nierenfunktion vom Nervensystem, Arch. exper. Path. u. Pharmakol. **73**:49, 1913; **77**: 122, 1914.

fashion. Despite these complexities, a fair body of evidence has been presented which implies that the most important stimulus for thirst is an increase in the effective osmotic pressure of the extracellular fluids or the necessary consequence of this phenomenon, cellular dehydration. Gilman [3] examined this problem in dogs by studying the rate and volume of ingestion of water after the injection of 20% solutions of sodium chloride or 40% solutions of urea, concentrations which are approximately isosmolar. The rate and total volume of water ingested were greater after the infusion of salt. Moreover, the volume of water ingested after the administration of the saline solutions was within 4% of the amount necessary to restore the tonicity of the body fluids to normal. The stimulus to thirst, therefore, was related to the effective osmotic pressure of the extracellular fluid or cellular dehydration, rather than to the total osmotic pressure per se. Thirst is also stimulated by the administration of hypertonic solutions of any other solute which cannot traverse the cell membranes freely. Holmes and Gregersen [4] stimulated thirst in dogs with the infusion of hypertonic solutions of sorbitol and dextrose. In these circumstances thirst was stimulated by an increase in the effective osmotic pressure of the extracellular fluids despite the fact that the concentration of sodium in these fluids was reduced. The receptor that measures the effective osmotic pressure responds to the sum total of this dimension and not to the particular contribution made by sodium and its salts. Hypertonicity of the fluids may be associated with thirst when the extracellular volume is contracted (water deprivation), as well as when it is expanded (injection of hypertonic solutions). In both instances intracellular volume is contracted. The most attractive hypothesis derived from these data is that some key structure is responsive to the tonicity of the extracellular fluid and that this osmoreceptor is stimulated by the dehydration of its cells. In experiments which are qualitatively similar to those performed on lower animals, Wolf [5] examined the influence of the tonicity of the extracellular fluids on the thirst mechanism in man. He calculated the relative decrease in cellular water content apparent at the time that the sensation of thirst was appreciated and reported this value to be 1.23 ± 0.48 %.

Holmes and Gregersen [4] were disturbed by the fact that their dogs demonstrated a lack of quantitative precision with respect to the volume of water ingested after the induction of hypertonicity of the body fluids. They did demonstrate, however, that, regardless of the fact that many of the animals drank less water than was necessary to restore the body fluids to isotonicity, any given dog drank larger volumes as the hypertonicity was made more intense. The lack of precision merely implies that all the osmostats are not set at the same level and that there are other factors that may condition the response. There is other evidence to support the contention that the alleviation of thirst is not always completely dependent on the restoration of a normal tonicity of the fluids of the body. Dogs with an esophageal fistula are temporarily satisfied after they have gulped about two and a half times

3. Gilman, A.: The Relation Between Blood Osmotic Pressure, Fluid Distribution, and Voluntary Water Intake, Am. J. Physiol. **120**:323, 1937.

4. Holmes, J. H., and Gregersen, M. I.: Observations on Drinking Induced by Hypertonic Solutions, Am. J. Physiol. **162**:326, 1950; Role of Sodium and Chloride in Thirst, ibid. **162**:338, 1950.

5. Wolf, A. V.: Osmometric Analysis of Thirst in Man and Dog, Am. J. Physiol. **161**: 75, 1950.

the deficit of water, despite the fact that none of this fluid enters the stomach. If water is placed directly into the stomach through a tube after the induction of a deficit of water, immediate drinking is inhibited in proportion to the filling of the stomach in the rat, hamster, and guinea pig.[6]

Although attention has, until recently, been focused largely on the role of tonicity and psychic factors in the control of thirst, there is a growing body of evidence to suggest that contraction of the extracellular fluids may, at times, induce a sensation akin to thirst.[7] This stimulus may be so potent as to override the usual tendency for hypotonicity of the body fluids to repress thirst. This may explain the excessive ingestion of water by dogs who are markedly hyponatremic but who are also depleted of salt.[8]

The areas in the central nervous system where stimuli eliciting thirst are integrated have not been completely described. There is, however, evidence to implicate the hypothalamus and, perhaps, the frontal lobes. Bilateral electrolytic lesions in the ventromedian nuclei of the hypothalamus of the rat are associated with hyperphagia and hypodipsia. These animals are chronically dehydrated and hypernatremic if their diets are dry and their water intake is dependent on drinking.[9] Adolph states that "injuries of certain regions of the cerebrum also enhance drinking."[10] A primary hyperdipsia has been observed in the monkey after a prefrontal lobotomy.[11] Since it is now clearly established that the thirst in diabetes insipidus is secondary to polyuria,[12] the lesions induced by Bellows and Van Wagenen [13] may very well represent another instance of primary disorder in the thirst mechanism.

An intact thirst mechanism, however, cannot serve as an effective guide in the regulation of fluid intake either in patients who are too ill and weak to complain of thirst or lift a pitcher of water, or in those who have a clouded state of consciousness or frank coma. In these circumstances a deficit of water must be diagnosed or anticipated by the physician in quantitative terms if the patient is to be protected from a severe distortion of the volume and tonicity of the body fluids. Moreover, in these seriously ill patients the difference between normal hydration and dehydration may be critical in determining the ultimate outcome.

Figure 1 describes an instance of the development of hypertonicity of the body fluids in three such patients.

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6. Bellows, R. T.: Time Factors in Water Drinking in Dogs, Am. J. Physiol. **125**:87, 1939. Towbin, E. J.: Gastric Distention as a Factor in the Satiation of Thirst in Esophagostomized Dogs, ibid. **159**:533, 1949. Adolph, E. A.: Thirst and Its Inhibition in the Stomach, ibid. **161**:374, 1950.

7. McCance, R. A.: Medical Problems in Mineral Metabolism, Lancet **1**:643, 704, 765, and 823, 1936.

8. Holmes, J. H., and Cizek, L. J.: Observations on Sodium Chloride Depletion in the Dog, Am. J. Physiol. **164**:407, 1951.

9. Stevenson, J. A. F.; Welt, L. G., and Orloff, J.: Abnormalities of Water and Electrolyte Metabolism in Rats with Hypothalamic Lesions, Am. J. Physiol. **161**:35, 1950.

10. Adolph, E. A.: Physiology of Man in the Desert, New York, Interscience Publishers, Inc., 1947, Chap. 15, p. 241.

11. Stevenson, J. A. F.; Welt, L. G.; Orloff, J., and Wall, P.: Unpublished data.

12. Swann, H. G.: Some Experiments on Salt and Water Metabolism in Diabetes Insipidus, Endocrinology **25**:288, 1939. Holmes, J. H., and Gregersen, M. I.: The Origin of Thirst in Diabetes Insipidus, Am. J. Med. **4**:503, 1948.

13. Bellows, R. T., and Van Wagenen, W. P.: The Relationship of Polydipsia and Polyuria in Diabetes Insipidus, J. Nerv. & Ment. Dis. **88**:417, 1938.

A portion of the hospital course of the first patient (E. T., C95723) is presented in the uppermost portion of this figure: A 56-year-old woman, who was admitted to the hospital on June 10, 1951, was known to have had severe hypertension for many years and had sustained several cerebrovascular accidents. Two weeks before admission aphasia and weakness of the left extremities developed. Five days before admission she began to cough and on the day of admission exhibited fever and lethargy and lapsed into coma. It was reported that her fluid intake had been adequate until the day of admission. She had hypertension, tachycardia, and fever. She was acutely ill and comatose and had evidences of dehydration. The retinal vessels were narrowed and tortuous; the heart was enlarged; there were signs of pneumonia at the base of the left lung, and the left arm and leg were flaccid. A chest roentgenogram revealed bilateral bronchopneumonia. The morning after admission it was found that the nonprotein nitrogen was 46 mg. per 100 cc., and that sodium was 147.5 mEq., potassium, 2.9

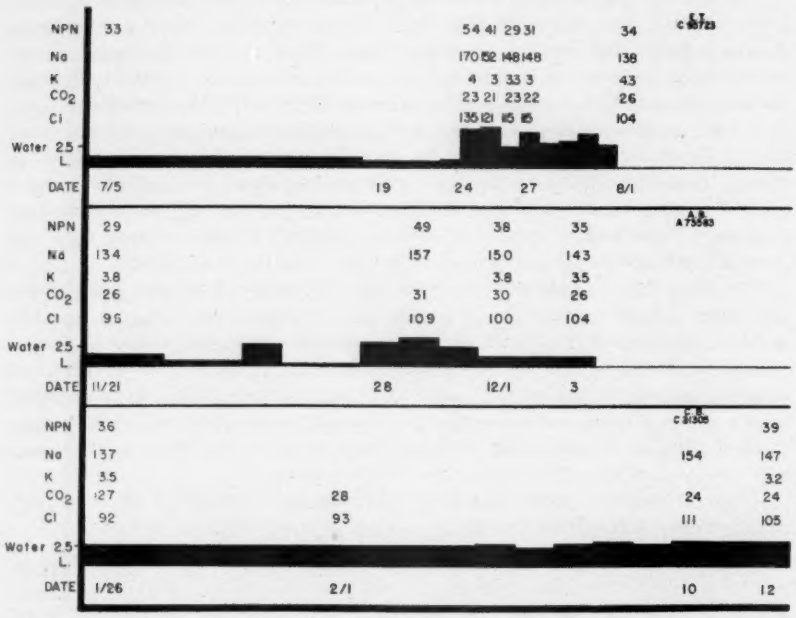

Fig. 1.—Development of hypertonicity of body fluids in three seriously ill patients with loss of consciousness. Nonprotein nitrogen (*NPN*) is expressed in milligrams per 100 cc. Sodium, potassium, carbon dioxide, and chloride are expressed in milliequivalents per liter.

mEq., bicarbonate, 20.7 mEq., and chloride, 112 mEq. per liter. The dehydration and renal decompensation responded to the administration of fluids, and the pneumonia improved with antibiotic therapy. Although she regained consciousness, intelligent contact with her environment was minimal. From July 5 to 14 she had an average daily fluid intake of 1,360 cc. This fell to a daily average of 1,220 cc. between July 14 and 20 and was still further reduced to a daily average of 930 cc. between July 20 and 24. On July 21 she had diarrhea which may have been due to the administration of terramycin directed at a urinary tract infection. The fever, which had been low grade, increased, and she became less responsive. It should be emphasized that this small average daily fluid intake occurred during the hot July weather in a patient who had some fever and who had had diarrhea. Analysis of blood drawn the morning of July 24 revealed a nonprotein nitrogen of 54 mg. per 100 cc. and sodium of 170

mEq., potassium of 4 mEq., bicarbonate of 23 mEq., and chloride of 135 mEq. per liter. This severe deficit of water was treated, and by Aug. 1 the chemical abnormalities had been corrected. On the morning of July 25 she was described as more responsive and having less diarrhea. She remained in the hospital until her death on Nov. 4, 1951. Despite the fact that the remainder of her course was complicated by the urinary tract infection, bronchopneumonia, intermittent periods of fever, and a continuous clouding of consciousness, attention to her fluid intake prevented a recurrence of the dehydration and azotemia. At postmortem examination she was found to have severe generalized and cerebral arteriosclerosis, with areas of encephalomalacia in the basal ganglia, and bronchopneumonia.

The second patient (A. B., A73583), a part of whose course is depicted in the middle section of Figure 1, was an 83-year-old man admitted to the hospital on Nov. 20, 1951. His complaints were cough, insomnia, weakness, and fever of two days' duration. He was known to have had hypertension and an enlarged heart, with congestive failure in April, 1950. At the time of the present admission his blood pressure was only 124/80. He had fever, appeared acutely ill, but was alert and cooperative. There were moderate changes in the retinal vessels; the heart was enlarged, and there were signs in the chest suggestive of pneumonia. A chest roentgenogram revealed cardiac enlargement, pulmonary congestion, left pleural effusion, and, probably, pneumonitis of both lower lobes. An analysis of blood drawn on Nov. 21 revealed normal values, except for a depressed concentration of total protein in the serum. Examination of the nurses' notes reveals the following: Nov. 22, "not taking fluids well; lethargic"; Nov. 24, "talking incoherently, very lethargic"; Nov. 25, "disoriented and progressively more unresponsive." His daily fluid intake averaged 1,350 cc. on Nov. 21 and 22, 585 cc. on Nov. 23 and 24, 2,875 cc. on Nov. 25, and 315 cc. on Nov. 26 and 27. The fluid intake was nil all day Nov. 28, and he was given 3,000 cc. of fluid from midnight until the early morning of Nov. 29. The chemical analyses of the patient's blood on this morning were reported to show 49 mg. of nonprotein nitrogen per 100 cc., 157 mEq. of sodium, 31 mEq. of bicarbonate, and 109 mEq. of chloride, per liter. The concentration of the total proteins in the serum had increased by 10%. He received 3,500 cc. of fluid on Nov. 29 and 2,450 cc. on Nov. 30; on the morning of Dec. 1 the nonprotein nitrogen was just within normal limits, but the deficit of water as evidenced by the concentration of sodium in the serum had been only partially corrected. It was not until Dec. 2 that the nurses' notes remarked that he was "more alert today," and on the following day the concentration of sodium was just at the upper range of the normal limits. He died on Dec. 5.

The third patient in this group (C. B., C21305) was a 43-year-old married woman who was admitted to the hospital in coma on Jan. 17, 1949. She had been found at 8 p. m. by her husband in an otherwise empty small bungalow. The gas stove was turned on; the windows were closed, and she is said to have had a "flushed complexion." At the time of her admission to the hospital, the blood pressure was unobtainable; the temperature was 102 F., the pulse rate, 100, and respiration rate, 24. She was deeply comatose and cyanotic. She did not appear dehydrated. The corneal reflex was present but diminished, and all four extremities were flaccid. Throughout the 30 days of her hospitalization she was almost continuously comatose. There was some improvement in the last week characterized by an ability to be aroused.

During the first nine days she was treated with fluids parenterally, and on Jan. 26 the chemical analyses of her blood gave normal results. On this day gavage feedings with 2,400 cc. of a high caloric liquid were begun. In addition, she received several hundred cubic centimeters of a 5% dextrose solution by gavage. Results of chemical analyses of her blood on several occasions up to and including Feb. 1 were normal. During this period she had had a low-grade fever which had begun to subside; but the elevation of temperature again increased, and on Feb. 3 it is noted that she sweated profusely. From Feb. 5 to 9, there was 18 to 20 gm. of salt added to the gavage feedings each day. Modest estimates of insensible loss of water and sweat added to the volume of urine easily equaled and probably exceeded the fluid intake during this period. On Feb. 10 the concentration of sodium in her serum was 154 mEq., of bicarbonate, 24 mEq., and of chloride, 111 mEq., per liter. The addition of the extra salt was discontinued and the fluid intake increased on this day. Two days later, the nonprotein nitrogen was found to be at the upper limits of normal and the sodium was

still elevated at a concentration of 147 mEq. per liter. The higher intake of fluid was maintained throughout the remainder of her course in the hospital, and there were no evidences of dehydration or hypernatremia at any subsequent examination.

These three patients are examples of the simplest type of dehydration—a deficit of water. Moreover, these deficits of water did not develop because urinary losses were excessive. They were simply the result of an inadequate intake of water in patients with some increase in the extrarenal loss of water in excess of salt as insensible and sensible perspiration. Had these patients been alert with access to water, they probably would have prevented the deficit by increasing the intake of water as a response to thirst, or, at least, they might have complained of thirst and been given appropriate volumes of water by one route or another. In the absence of these aids from the patient, the physician must use his knowledge of the quantitative aspects of water exchange and make certain that appropriate volumes of fluid have been administered.[14]

This same sequence of events may be accelerated or exaggerated if, for some particular reason, the loss of water as urine is increased. The existence of an excessive flow of urine may be unrecognized if the patient is unconscious and incontinent, or may be mistakenly interpreted as a sign of good renal function if it is not immediately recognized that the urine output, alone, is equal to or in excess of the total fluid intake.

The volume of urine formed is the net result of filtration and tubular reabsorption. The latter is influenced by at least two processes: (1) the action of antidiuretic hormone, which selectively promotes the reabsorption of water in the distal tubules, and (2) the load of nonreabsorbed solutes, which inhibits the reabsorption of water in the proximal as well as the distal tubules.[15] About 80% of the filtered solutes are actively reabsorbed in the proximal tubule, as a consequence of which an osmotic gradient is set up between the tubular lumen and the extracellular fluid. As a result, tubular water diffuses passively through the tubular membrane into the extracellular compartment. These processes maintain the total solute concentration within the lumen of the proximal nephron isotonic with glomerular filtrate, although the composition of the tubular fluid is markedly altered.

14. A deficit of water in excess of salt is clearly reflected in most patients by a distinct elevation in the concentration of sodium in the serum. However, it should be emphasized that this may not obtain in the presence of hyperglycemia. Glucose does not penetrate the cell membrane freely and, hence, it exerts an effective osmotic force. An increase in the concentration of glucose in extracellular fluids promotes a transfer of water from cells to the extracellular compartment, thus causing a depression of the concentration of sodium in this compartment by dilution. Therefore, the concentration of sodium must be interpreted with knowledge of the concentration of glucose in the blood if there is any reason to suspect hyperglycemia. Three hundred sixty milligrams of glucose per liter (2 milliosmoles) corresponds to 1 mM. (2 millosmoles) of sodium chloride or sodium bicarbonate.

15. These concepts are largely derived from micropuncture studies of the tubules of amphibian kidneys under special experimental conditions (Walker, A. M.; Hudson, C. L.; Findley, T., Jr., and Richards, A. N.: Am. J. Physiol. **118**:121, 1937). It is proper, therefore, to display some caution in accepting these concepts at face value with reference to the function of the mammalian kidney in general and of the human kidney in particular. Perhaps the most serious question relates to the topographical division of specific renal tubular functions. The existence of the various tubular mechanisms is most important; the specific sites of these several activities are less relevant. However, since the only available data suggest a topographical division of function, this terminology is used in this discussion.

Since the reabsorption of water in the proximal tubule is passive, the volume delivered to the distal tubule is a function of the extent to which the solutes have been reabsorbed in the proximal portion of the nephron. The reabsorption of solute will be less if the filtrate has a high concentration of some substance whose reabsorption is limited, e. g., glucose or urea, or if the proximal reabsorption of salt is diminished for one reason or another. The final volume of urine is determined in the distal tubule, where solutes and water may be treated independently. This independence, however, has a limit in that there is an osmotic ceiling beyond which the urine cannot be concentrated. The reabsorption of water is under the control of the antidiuretic hormone of the posterior pituitary gland. When usual volumes of urine are delivered to the distal tubule and there is maximal antidiuretic hormone activity, water is reabsorbed to produce a highly concentrated urine. The concentration of total solutes in the urine may be as high as 1,400 milliosmoles per liter. The extent to which the urine is concentrated is partially dependent on the nature of the major urinary solute, the rate of flow of urine, and other factors. When large volumes of tubular urine are delivered from the proximal to the distal nephron, the final urine concentration may be much less than 1,400 milliosmoles per liter despite maximum antidiuretic hormone activity. In summary, there appears to be a maximal rate of reabsorption of water in the distal tubule, as well as a maximum concentration that can be achieved. The presentation of a large solute load for excretion may promote a large flow of urine that is dilute despite the coexistence of dehydration.[16]

Verney and his colleagues [17] have demonstrated in a brilliant series of investigations that the secretion of the antidiuretic hormone is promoted by an increase in the effective osmotic pressure of the fluid bathing a receptor that lies somewhere within the distribution of the internal carotid artery. An injection of a small volume of hypertonic saline, sucrose, or dextrose solution into the internal carotid artery of a dog undergoing a diuresis of water is soon followed by a decrease in the rate of excretion of urine with an increased concentration of solutes. This does not follow an isosmolar injection of urea. This osmoreceptor appears to behave in much the same way as does the receptor involved in the sequence of events leading to the sensation of thirst. The stimulus is transmitted along the path leading from the supraoptic nucleus to the posterior pituitary gland and incites the secretion of antidiuretic hormone (ADH). An interruption of certain parts of this neural path by any lesion eliminates the ability to secrete this hormone.[18] Other stimuli that may

16. Walker, A. M.; Hudson, C. L.; Findley, T., Jr., and Richards, A. N.: The Total Molecular Concentration and the Chloride Concentration of Fluid from Different Segments of the Renal Tubule of Amphibia, Am. J. Physiol. **118**:121, 1937. Richards, A. N.: Croonian Lecture: Processes of Urine Formation, Proc. Roy. Soc., London, s.B **126**:398, 1938. Smith, H. W.: The Excretion of Water, Bull. New York Acad. Med. **23**:177, 1947. Wesson, L. G., Jr.; Anslow, W. P., Jr., and Smith, H. W.: The Excretion of Strong Electrolytes, ibid. **24**:586, 1948. Smith, H. W.: The Kidney: Structure and Function in Health and Disease, New York, Oxford University Press, 1951. Wolf, A. V.: The Urinary Function of the Kidney, New York, Grune & Stratton, Inc., 1950.

17. Verney, E. B.: Croonian Lecture: The Antidiuretic Hormone and the Factors Which Determine Its Release, Proc. Roy. Soc., London, s.B **135**:25, 1947.

18. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance, Ann Arbor, Mich., Edwards Bros., Inc., 1938.

promote secretion of antidiuretic hormone when this system is intact are emotion and, perhaps, a decrease in blood volume.[19]

The certain clinical differentiation between diabetes insipidus and a primary polydipsia cannot be made without resort to examinations which specifically test the integrity of the supraopticohypophyseal system. This is accomplished by presenting the primary physiologic stimulus for the secretion of antidiuretic hormone, hypertonicity of the body fluids. Restriction of water for as long a period as the patient will tolerate will lead to hypertonicity. If the specific gravity of the urine rises to 1.010 or more in these circumstances, it is most unlikely that the patient is suffering with diabetes insipidus.[20] However, although simple, this procedure is not without some risk. The loss of water and, therefore, volume may be large enough in the patient with diabetes insipidus to promote a state of peripheral vascular collapse. Hickey and Hare devised a test which has considerable merit.[21] They recommend the administration of a large volume of water in the first hour to achieve a maximum diuresis. When this is established, the patient is given an infusion with a 2.5% solution of salt. This presents the physiologic stimulus of hypertonicity without a water deficit. The normal response is an antidiuresis, whereas the patient with diabetes insipidus will have either no change in urine flow or an increase. The increase in flow in a patient with diabetes insipidus is a reflection of the larger volume of fluid delivered to the distal tubule.

The following case illustrates what may happen to a patient in whom acute diabetes insipidus develops if it goes unrecognized even for a short time (Fig. 2).

This patient (M. B., B91214) had a craniopharyngioma, part of which had been removed in December, 1947. She was readmitted to the hospital on April 2, 1948, with the chief complaints of increasing headache, nausea, and vomiting. Results of chemical analyses of the blood made on admission were within normal limits except for a nonprotein nitrogen of 42 mg. per 100 cc. The day following admission an exploratory operation was done, and an occluding cystic mass was removed from the third ventricle. On the day of operation she received 3,400 cc. of fluid. In addition to an unknown volume of urine voided incontinently, the recorded urine output was 3,200 cc. The following morning the blood pressure was low, and her general condition was reported as poor. During this morning she received 650 cc. of fluid, but her urine output was 1,100 cc. and it had a specific gravity of 1.005. At 3 p. m. the concentration of sodium in the serum was 171.5 mEq. per liter. She was treated with the intravenous administration of 5% dextrose solution in water and periodic injections of posterior pituitary (pituitrin®). During the next few days there was some reexpansion of body water, as evidenced by decreasing concentrations of electrolytes in the serum and a falling hematocrit. The use of posterior pituitary was complicated by side-reactions, and after

19. (*a*) Rydin, H., and Verney, E. B.: The Inhibition of Water Diuresis by Emotional Stress and by Muscular Exercise, Quart. J. Exper. Physiol. **27**:343, 1938. (*b*) Welt, L. G., and Orloff, J.: The Effects of an Increase in Plasma Volume on the Metabolism and Excretion of Water and Electrolytes by Normal Subjects, J. Clin. Invest. **30**:751, 1951. (*c*) Martin, S. J.; Herrlich, H. C., and Fazekas, J. F.: Relation Between Electrolyte Imbalance and Excretion of an Antidiuretic Substance in Adrenalectomized Cats, Am. J. Physiol. **127**: 51, 1939. (*d*) Leaf, A., and Mamby, A. R.: An Antidiuretic Mechanism Not Regulated by Extracellular Fluid Tonicity, J. Clin. Invest. **31**:60, 1952.

20. Brown, W. E., Jr., and Rynearson, E. H.: A Procedure for the Diagnosis of Diabetes Insipidus, Proc. Staff Meet., Mayo Clin. **19**:67, 1944.

21. Hare, R. S.; Hare, K., and Phillips, D. M.: The Renal Excretion of Chloride by the Normal and by the Diabetes Insipidus Dog, Am. J. Physiol. **140**:334, 1943. Hickey, R. C., and Hare, K.: The Renal Excretion of Chloride and Water in Diabetes Insipidus, J. Clin. Invest. **23**:768, 1944.

two days of inadequate fluid administration the dehydration was almost as extreme as it had been on the first postoperative day. Her condition went gradually downhill, and she died on April 15. At postmortem examination a tumor was found compressing the floor of the third ventricle.

This case is an excellent example of the rapid development of severe dehydration, hypertonicity of an unusual degree, and peripheral vascular collapse in a patient with acute diabetes insipidus. The situation was not immediately apparent because the unconscious patient was unable to complain of thirst. The hypertonicity became extreme owing to the loss of water in urine due to the absence of the antidiuretic hormone.

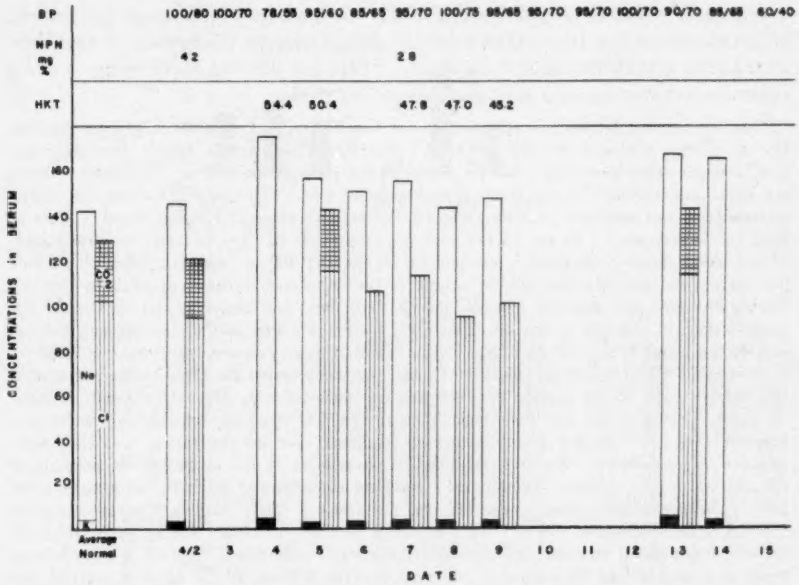

Fig. 2.—Serum electrolyte concentrations in milliequivalents per liter, nonprotein nitrogen values in milligrams per 100 cc., and blood-pressure readings (*BP*) in patients with acute diabetes insipidus. *HKT* is hematocrit in volumes per cent.

Patients with medical and surgical neurologic lesions have been observed to have severe hypertonicity of the body fluids in the absence of diabetes insipidus. Such patients have been reported on by Allott, Luetscher and Blackman, Sweet and associates, and MacCarty and Cooper.[22] It is difficult to make a complete analysis

22. Allott, E. N.: Sodium and Chloride Retention Without Renal Disease, Lancet **1**:1035, 1939. Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. **18**:741, 1943. Sweet, W. H.; Cotzias, G. C.; Seed, J., and Yakovlev, P. I.: Gastrointestinal Hemorrhages, Hyperglycemia, Azotemia, Hyperchloremia, and Hypernatremia Following Lesions of the Frontal Lobe in Man: The

(Footnote continued on next page)

of the balance of water and electrolytes in these cases. They may not all represent dehydration. It is conceivable that certain cerebral lesions may be responsible for an abnormal tonicity of the body fluids; this could result from a primary increase in cellular osmolar concentration. There is some support for such a hypothesis in the report of an investigation by Lewy and Gassman.[23] These investigators observed a significant and sustained elevation in the concentration of chloride in the serum of cats following unilateral stimulation of one of the hypothalamic nuclei. However, the fact that this clinical picture of severe water deficit with unusual hypernatremia has been reported so frequently among patients with neurologic disorders may have no more specific relation to the central nervous system than the fact of a clouded state of consciousness which limits the ability to experience and express the sensation of thirst. The basic pathogenesis of this condition may be common to a variety of circumstances but is usually limited in degree because fluid intake is regulated in accordance with the dictates of thirst. There has been an opportunity to make some observations on two such patients in this clinic.

Twenty minutes before his admission to the hospital on Oct. 7, 1949, a 44-year-old man (F. S., 30108) was shot through the head. The wound of entrance was in the midfrontal area, and the bullet pursued a posterior course to the right of the midline. It lodged between the scalp and the skull in the right parieto-occipital area. He was unconscious and febrile on admission and remained so throughout his illness. He received between 2 and 3 liters of fluid and an average of 10 gm. of salt each day until Oct. 12. On this date an examination of his blood revealed nonprotein nitrogen of 50 mg. per 100 cc. and 117 mEq. of chloride per liter in the serum. The specific gravity of the urine was recorded as 1.022 on Oct. 11. During the next five days he received a little more fluid and less salt, and on Oct. 17 the concentration of chloride in the serum was 112.1 mEq. per liter and the nonprotein nitrogen was 46 mg. per 100 cc. In the next 10 days he received an average daily intake of 2,340 cc. of fluid and 6.5 gm. of sodium chloride. During this same period the blood pressure gradually fell, until on Oct. 25 the systolic pressure was less than 100 mm. Hg. An accurate measure of the volume of urine was not available until Oct. 24, when an indwelling catheter was inserted (Fig. 3). In the three-day period beginning Oct. 24 the patient was in definite negative water balance. The concentrations of electrolytes in the serum on the morning of Oct. 27 were 173.1 mEq. of sodium, 131.7 mEq. of chloride, and 2.7 mEq. of potassium per liter. The nonprotein nitrogen was 188 mg. per 100 cc. That morning there was a urine volume of approximately 200 cc., with a specific gravity of 1.012. In the early afternoon he was in peripheral vascular collapse with no apparent urine flow. At 3:30 p. m. a balance study was started. In the next five hours he received 6 liters of 5% dextrose solution and 90 mEq. of potassium. During this period he excreted 1,820 cc. of urine with a specific gravity of 1.022. Despite the unusually high concentration of sodium in the serum, the concentration of this ion in the urine was only 17.6 mEq. per liter. The total solute concentration of this urine was 515 milliosmoles per liter.[24] The concentration of sodium in the serum had fallen from 175.1 to 144.5 mEq. per liter by 8:45 p. m., but the hematocrit had increased from 26 to 31 vol.%. At 6 p. m. the rate of urine flow was about 600 cc. an hour. Posterior pituitary powder was applied to the nasal mucosa at 6 and 7 p. m., and

Frontal Lobe, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:795, 1948. MacCarty, C. S., and Cooper, I. S.: Neurologic and Metabolic Effects of Bilateral Ligation of the Anterior Cerebral Arteries in Man, Proc. Staff Meet., Mayo Clin. **26**:185, 1951. Cooper, I. S., and MacCarty, C. S.: Unusual Electrolyte Abnormalities Associated with Cerebral Lesions, ibid. **26**:354, 1951.

23. Lewy, F. H., and Gassman, F. K.: Experiments on the Hypothalamic Nuclei in the Regulation of Chloride and Sugar Metabolism, Am. J. Physiol. **112**:504, 1935.

24. Total solute concentration in the urine was estimated from twice the sum of the concentrations of sodium, potassium, and ammonia, plus urea and glucose.

at 8:30 p. m. the rate of excretion of urine had decreased to about 250 cc. an hour. During the next 12 hours he was given another 2 liters of 5% dextrose solution, but no more pituitary substance, since the urine flow was not excessive. In this second period the volume of urine was 1,440 cc. with a concentration of sodium of 6.2 mEq. per liter and a total solute concentration of 630.6 milliosmoles per liter. At 8:30 the following morning the concentrations of electrolytes in the serum were as follows: sodium 152 mEq., chloride 111.5 mEq., bicarbonate

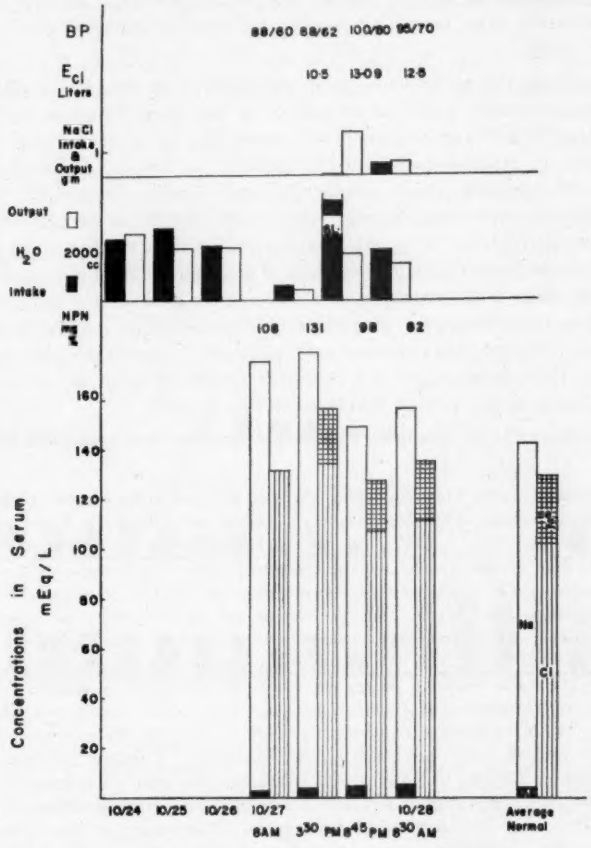

Fig. 3.—Development of hypertonicity of body fluids in absence of diabetes insipidus in patient with serious neurologic lesion. E_{Cl} indicates extracellular space.

23.8 mEq., and potassium 4.8 mEq., per liter. The hematocrit was 29.7 vol.%, and the nonprotein nitrogen had fallen from 131 to 82 mg. per 100 cc. The lower concentration of sodium in the serum at 8:30 p. m. was related to the hyperglycemia, aggravated by the rapid administration of dextrose to a subject who apparently had an impaired tolerance for carbohydrate. It was not known at the time that the concentration of dextrose in the serum was 360 mg. per 100 cc. at the beginning of the balance period. Likewise, the glycosuria probably

contributed to the rapid rate of excretion of urine. The increase in the hematocrit at a time that the body fluids had been expanded was the result of swelling of the red cells.

The urinary specific gravity of 1.022 on Oct. 12 at a time that the concentration of chloride in the serum was 117 mEq. per liter renders diabetes insipidus as a cause of the presumed dehydration quite unlikely. During the period that accurate measurements of urine volume were available, it is clear that the patient was in negative water balance. This suggested that he might have had diabetes insipidus after a reexploration of the cerebral wound on Oct. 19. It was with this in mind that the posterior pituitary preparation was used. Postmortem examination of the brain failed to reveal any lesion in the region of the supraoptico-hypophyseal system.

The answer to this problem may lie in the nature of the fluid this patient received. In the gavage feedings which were started the day after admission he received a daily average of 159 gm. of protein at a time that he must certainly have been experiencing the reaction to injury characterized by inability to store nitrogen.[25] This amount of protein would provide 26.5 gm. of urea nitrogen per day, and it is very likely that this would be augmented to the extent that he may have been in negative nitrogen balance. This urea nitrogen and the daily average of 8.1 gm. of salt provide a minimal solute load for excretion of more than 1,200 milliosmoles per day. The average daily fluid intake minus a conservative estimate for insensible loss of water leaves about 1 liter of water each day for urine during the first 20 days. Even if the urine had been continuously maximally concentrated, he could hardly have escaped the development of a deficit of water. It is altogether possible that the dehydration in this patient developed in this manner.

Examination of the data from another patient may shed additional light on this problem.

J. C. (C37667) was a 43-year-old man who was admitted to the hospital on Feb. 8, 1950, with the chief complaint of left-sided weakness. Except for a history of hypertension he was apparently well until Feb. 5, 1950, when he was involved in an automobile accident. There was no period of unconsciousness, but he claimed to have been "roughed up" while in jail after the accident. On admission his blood pressure was 198/148, pulse rate 102, respiration rate 26, and temperature 101 F. He was restless and uncooperative; his speech was clear but rambling, and there were frequent self-contradictions. There was a contusion with swelling around the left orbit. The left optic disk was normal, and the right could not be well visualized. There was weakness of the grip of the left hand and of dorsiflexion of the left foot. Within a few hours after admission he lapsed into a deep slumber with Cheyne-Stokes respiration. The blood pressure increased, and the pulse rate fell. He was extremely lethargic but could be aroused. His speech had become incoherent. A lumbar puncture revealed an initial pressure of 270 mm. of water, which fell to 160 mm. after the withdrawal of 5 cc. of slightly yellow and turbid fluid. On Feb. 9 a hematoma was evacuated from the right hemicranium. This was followed by a transient period of improvement, after which he again became comatose. Reexploration with evacuation of more hematoma was performed on the following day. He improved, was able to answer questions, but had a left hemiparesis. The nonprotein nitrogen on the morning after admission was 47 mg. per 100 cc., and this rose to 123 mg. per 100 cc. on Feb. 13 (Fig. 4). The fluid intake averaged about 2,500 cc., but urine volumes were unknown because of incontinence. However, the nonprotein nitrogen began to fall and was reduced to 85 mg. per 100 cc. on Feb. 16. On the following day the patient became somnolent and remained in that state throughout the remainder of the study period.

25. Cuthbertson, D. P.: Observations on the Disturbance of Metabolism Produced by Injury to the Limbs, Quart. J. Med. **1**:233, 1932. Peters, J. P.: Nitrogen Metabolism in Acute and Chronic Disease, Ann. New York Acad. Sc. **47**:327, 1946; Effect of Injury and Disease on Nitrogen Metabolism, Am. J. Med. **5**:100, 1948.

On Feb. 16 a tube was inserted into the stomach, and the patient received an average of 2,100 cc. of fluid and 94 gm. of protein a day during the next four days. Within 48 hours the nonprotein nitrogen had increased to 103 mg. per 100 cc., and evidences of a water deficit were discernible in the increased concentration of sodium and total proteins in the serum. In the next few days the nonprotein nitrogen rose still higher, as did the concentrations of sodium and total proteins in the serum. The protein feedings had been completely discontinued by Feb. 22 and the fluid intake increased. There was a prompt reduction in the concentrations of nonprotein nitrogen, total proteins, sodium, and chloride. On March 2 the nonprotein nitrogen was within normal limits at 38 mg. per 100 cc.

The decline in concentration of nonprotein nitrogen prior to the institution of protein feedings suggests that initial dehydration and renal decompensation were

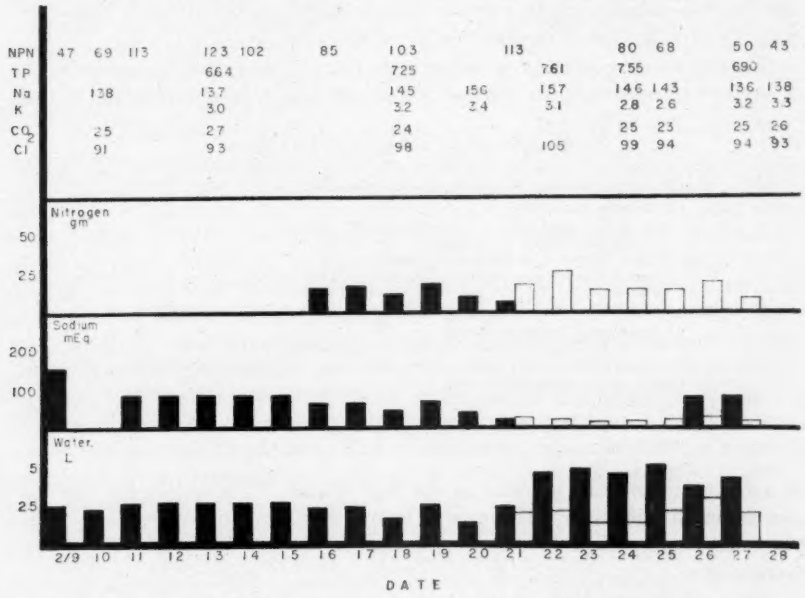

Fig. 4.—Development of hypertonicity of body fluids in absence of diabetes insipidus in patient with serious neurologic lesion. Black columns indicate intake and white columns output. Nonprotein nitrogen is expressed in milligrams per 100 cc., and total protein (*TP*) is expressed in grams per 100 cc. Electrolytes are expressed in milliequivalents per liter.

improving. Very promptly after the institution of feedings of protein, the nitrogen of which could not be stored, a deficit of water was incurred. As soon as the protein was eliminated from the diet and larger volumes of fluid administered, this entire process was reversed. As in the previous case, the concentration of sodium in the urine was extremely low (7 to 10 mEq. per liter) despite a high concentration of this ion in the serum.

A consideration of the physiologic consequences of a water deficit provides an amazing display of a coordinated and well-integrated series of responses oriented toward the prevention of any greater sacrifice of fluid volume than is absolutely

necessary. These responses involve both internal and external exchanges of electrolytes and water (Table).

The earliest and probably most significant alteration in the internal environment associated with a deficit of water is an increase in the concentration of sodium in the extracellular fluid. Since the cells allow the free passage of water, the effective osmotic pressure in both major fluid compartments must be equal, and there is an immediate transfer of water from the cells. This provides a mechanism for a contribution to the deficit of water by both compartments and thus spares the extracellular fluid volume to some extent.

Cellular dehydration may be responsible for an increased rate of excretion of potassium. This may promote a release of this ion by the cells, and to the extent that this may decrease cellular osmolar concentration it may contribute a little more water to offset the deleterious effects of the dehydration.[26]

Another response relates to a change in the rate of loss of insensible perspiration. It has been demonstrated that the rate of insensible loss of water is inversely related

The Consequences of a Deficit of Body Water

A. Increase in concentration of sodium in extracellular fluid
  1. Cellular dehydration
    a. Decreases rate of insensible loss of water
    b. Retards rate of sweating
    c. Gives rise to sensation of thirst
  2. Stimulation of osmoreceptor → secretion of ADH → increased renal tubular reabsorption of water
B. Decrease in volume of all the body fluids
  1. Contraction of plasma volume
    a. Promotes increased renal tubular reabsorption of salt
    b. Promotes antidiuresis (presumably via posterior pituitary secretion of ADH)
C. Increase in oncotic pressure of plasma
  1. Stimulation of "oncoreceptor" (?)
    a. Increases tubular reabsorption of salt
    b. Increases tubular reabsorption of water

to the effective osmotic pressure of the body fluids.[27] The implication that the mechanism of this loss of water may be just as dependent on vapor pressure as is the rate of evaporation of water from a saline solution in an open vessel is most intriguing.

The centers and tracts in the central nervous system that are involved in temperature control have been well established by Ranson.[28] The centers regulating sweating are located in the anterolateral portions of the hypothalamus between the levels of the optic chiasm and the anterior commissure. The local application of heat promotes the discharge of impulses to the centers controlling the motor activities necessary to eliminate body heat. Sweating is related in some fashion to the effective osmotic pressure of the body fluids. This influence was described

26. Elkinton, J. R., and Winkler, A. W.: Transfers of Intracellular Potassium in Experimental Dehydration, J. Clin. Invest. **23**:93, 1944.

27. Gilman, A., and Barbour, H. G.: The Relation Between Blood Osmotic Pressure and Insensible Weight Loss, Am. J. Physiol. **104**:392, 1933. Ginandes, G. J., and Topper, A.: Insensible Perspiration in Children: The Influence of Salt, Am. J. Dis. Child. **55**:1176, 1938.

28. Ranson, S. W.: The Hypothalamus: Regulation of Body Temperature, Baltimore, Williams & Wilkins Company, 1940, Chap. 11.

as long ago as 1911 by Montuori [29] and later by Nishibori.[30] Dantos [31] reported that the threshold at which sweating or polypnea begins (depending on which mechanism is responsible for heat loss) is raised when animals are infused with hypertonic solutions of sodium chloride. Amatruda [32] has recently reexamined the influence of volume and tonicity of the body fluids on the secretion of thermal sweat in normal young adult men. He demonstrated quite clearly that the induction of hypertonicity of the body fluids by the infusion of a 5% solution of salt promoted an increase in the latent period (the interval between exposure to the heat stress and the onset of sweating) and a decrease in the rate of secretion of sweat.

The relationship of the sensation of thirst to the effective osmotic pressure of the body fluids has already been described. In the conscious and free state this becomes the most important element in the prevention of a serious deficit of water.

Lastly, the increased tonicity of the body fluids becomes an effective agent in supporting the conservation of body water by promoting the secretion of the antidiuretic hormone of the posterior pituitary gland. This permits the most efficient utilization of water for the excretion of the solutes in the urine.

Another consequence of the loss of fluid from the body is an increase in the concentration of those substances which contribute the osmotic pressure that is effective in determining the distribution of fluid between the plasma and the interstitial fluid compartment, the serum proteins. This provides particular protection to that volume of fluid which is most immediately concerned with the maintenance of life. A rise in the oncotic pressure of the plasma in the normal subject has been demonstrated to lead to an increased renal tubular reabsorption of salt and water.[33] The effect on salt is not mediated via the adrenal cortex,[19b] and the increased reabsorption of water is independent of the secretion of antidiuretic hormone by the posterior pituitary gland.[34] It has been postulated that there may be an oncoreceptor [19b] within the vascular tree with characteristics of permeability similar to those of the vascular endothelium, which would allow the fact of an increasing oncotic pressure to be registered. The importance to the conservation of volume contributed by the reabsorption of salt and water through this mechanism cannot be evaluated at this time.

Despite these several processes that are aimed at the conservation of fluid, to the extent that there is a deficit of water there must be a contraction of the body fluids. A decrease in the volume of the plasma promotes an increase in the tubular reabsorption of salt which is reflected in the very low concentrations of these ions in the urine of the patients whose course has just been described. This response

29. Montuori, A.: Relation Between Osmotic Pressure and Sweat Excretion, Arch. Physiol. **9**:439, 1911; Chem. Abstr. **6**:2465, 1912.

30. Nishibori, cited by Kuno, Y.: The Physiology of Human Perspiration, London, J. A. Churchill, Ltd., 1934, p. 235.

31. Dantos, S. P.: Über den Mechanismus der Wärmeregulation, Arch. ges. Physiol. **241**: 612, 1939.

32. Amatruda, T. T., and Webb, L. G.: A Study of the Secretion of Electrolytes in Thermal Sweat, to be published.

33. Welt and Orloff.[19b] Goodyer, A. V. N.; Relman, A. S., and Peterson, E. P. Some Effects of Albumin Infusions on Renal Function and Electrolyte Excretion in Normal Man, J. Appl. Physiol. **1**:671, 1949.

34. Petersdorf, R., and Welt, L. G.: The Influence of an Increase in Colloid Osmotic Pressure on the Metabolism and Excretion of Water, unpublished data.

to a contracted volume has been described by Peters as the dehydration reaction.[35] It has certain favorable consequences. The maximum reabsorption of salt accentuates the hypertonicity of the extracellular fluid and thus reinforces all the favorable responses to this alteration. In addition, by its virtually complete removal from the tubular fluid, salt is eliminated as a solute for excretion and thus saves some water from being lost to the urine.

It is not at all clear just how the fact of a contracted volume is recorded. The ultimate consequence of this stimulus, however, may be the secretion of an adrenal cortical hormone that enhances the renal tubular reabsorption of sodium. It is clear that the central nervous system may be involved in this sequence of events, if only by virtue of the residence therein of the anterior pituitary gland, whose adrenocorticotropic hormone may be necessary for this end-result. The experiments of Brun, Knudsen, and Raaschou, Harrison and his associates, Strauss and his co-workers, and others have each directed attention to some structure in the cephalad portion of the body, presumably intracranial, which has intimate relationships to the regulation of the excretion of salt.[36] The passive erect posture promotes an increased tubular reabsorption of salt, which appears to be dependent, in great part at least, on an intact adrenal cortex.[37] The changes in excretion of salt associated with the supine and sitting posture have fortified these other investigations. Harrison's group has demonstrated that the decreased rate of excretion of salt in the sitting posture may be partially prevented by applying pressure of the order of 20 mm. Hg about the neck. This same group of investigators has also reported that the decline in the rate of excretion of sodium promoted by the venesection of 2.5 cc. of blood per kilogram of body weight from sitting subjects can be prevented by similar compression of the neck.[38] All these data suggest that one of the functions of a decrease in plasma volume that serves as a stimulus for the increased tubular reabsorption of salt is the volume of fluid in some key structure within the cranial cavity.

The stimuli to which the anterior pituitary gland is responsive are not at all well understood. It is, of course, clear that its destruction by trauma, neoplasm,

35. Elkinton, J. R., and Taffel, M.: Prolonged Water Deprivation in the Dog, J. Clin. Invest. **21**:787, 1942. Peters, J. P.: Sodium, Water, and Edema, J. Mt. Sinai Hosp. **17**: 159, 1950.

36. Brun, C.; Knudsen, E. O. E., and Raaschou, F.: The Influence of Posture on the Kidney Function, Acta med. scandinav. **122**:315 and 332, 1945. Lewis, J. M., Jr.; Buie, R. M.; Sevier, S. M., and Harrison, T. R.: The Effect of Posture and of Congestion of the Head on Sodium Excretion in Normal Subjects, Circulation **2**:822, 1950. Viar, W. N.; Oliver, B. B.; Eisenberg, S.; Lombardo, T. A.; Willis, K., and Harrison, T. R.: The Effect of Posture and of Compression of the Neck on Excretion of Electrolytes and Glomerular Filtration: Further Studies, ibid. **3**:105, 1951. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: "Water Diuresis" Produced During Recumbency by the Intravenous Infusion of Isotonic Saline Solution, J. Clin. Invest. **30**:862, 1951.

37. Welt, L. G.: The Effects of the Passive Erect Posture on the Rates of Excretion of Salt and Water in the Adrenal Insufficient Subject, unpublished data.

38. Lombardo, T. A.; Eisenberg, S.; Oliver, B. B.; Viar, W. N.; Eddleman, E. E., and Harrison, T. R.: Effects of Bleeding on Electrolyte Excretion and on Glomerular Filtration, Circulation **3**:260, 1951.

or any other lesion may be followed by secondary adrenal cortical insufficiency and its attendant abnormalities in the metabolism and excretion of electrolytes and water.

This problem is illustrated by the course of a 73-year-old woman (M. B. DeF., C24856) who was first admitted to the hospital on April 17, 1949 (Fig. 5). Investigation of her complaints of headache, vomiting, anorexia, and weight loss led to a diagnosis of chromophobe adenoma of the pituitary. On April 27 a course of deep x-ray therapy was begun and was completed on May 3. After a total dose of 856 r the patient was discharged. She was readmitted three days later because of weakness. On admission her blood pressure, which had previously been elevated, was 90/55. She did not appear to be in distress, but on the following day the nurse noted that the "patient looks washed out." Nausea, vomiting, and

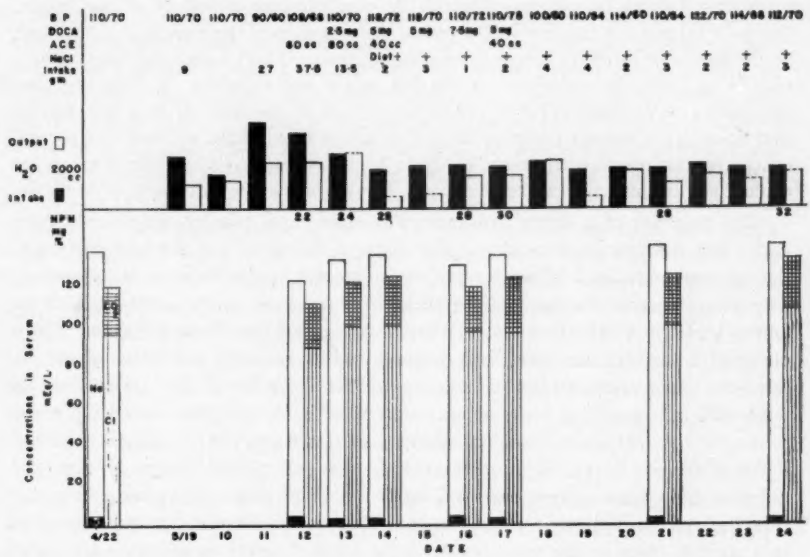

Fig. 5.—Development of hypertonicity of body fluids in secondary adrenal cortical insufficiency. *ACE* is adrenal cortex extract.

hiccoughs developed. At 2 a. m. on May 12 she had a sudden episode of weakness and perspired profusely, and the blood pressure was 80/50. A half-hour later this had risen to 108/68. That morning the concentration of sodium in the serum was 126.3 mEq. per liter, and by 3:30 p. m. it had fallen still further to 119.5 mEq. per liter despite the administration of 1 liter of isotonic sodium chloride solution in the interval. She was treated vigorously for adrenal cortical insufficiency with almost 4 liters of fluid containing 37.5 gm. of salt and 60 cc. of aqueous adrenal cortex extract. On the following morning, May 13, the concentration of sodium in the serum was 130.8 mEq. per liter, and there had been a corresponding increase in the concentration of chloride in the serum from 90.3 to 100.5 mEq. per liter. On this day she was given 2,750 cc. of fluid, 13.5 gm. of salt, 80 cc. of adrenal cortex extract, and 2.5 mg. of desoxycorticosterone acetate. During the next few days she ate a hospital diet to which had been added some extra salt. She received daily injections of desoxycorticosterone acetate until May 17, when pellets were implanted.

Any patient with such a tumor should be vigorously investigated from the standpoint of possible early adrenal cortical insufficiency. Although these patients may have no signs or symptoms of adrenal insufficiency in ordinary circumstances, they may progress rapidly into a life-threatening stage of cortical insufficiency as the result of an infection, accidental trauma, or an operative procedure. The concentrations of sodium and chloride in the serum are informative only if they are depressed. The careful study of the response to salt deprivation is much more informative. This, too, must be interpreted with caution, and observations must be made regarding loss of weight and the actual balance of salt as calculated from the intake and urine excretion, in addition to determinations of the concentrations of sodium and other electrolytes in the serum. It must be recalled that, although a negative balance of salt may depress the concentration of sodium in the serum, this very decrease in tonicity will suppress the secretion of the antidiuretic hormone by the posterior pituitary gland, promoting diuresis. This consequent loss of water may be of sufficient magnitude, if the salt loss is not excessive, to raise the concentrations of sodium and chloride in the serum to normal. If it is not known that there was a definite negative balance of salt or that weight was lost, the normal concentrations of electrolytes are likely to be interpreted to mean that there is no evidence of adrenal cortical insufficiency. This error may be costly and is avoidable.

The question of a direct neural regulation of renal tubular activity has been under investigation for some time. The work of Bernard [1] and the later investigation of Jungmann and Meyer [2] serve as landmarks in the study of this problem. The latter workers investigated the effect of a puncture lesion in the floor of the fourth ventricle a little forward of what is now called the eminentia teres. They observed a polyuria associated with an increased excretion of salt in the urine. A salt-poor diet diminished but did not abolish the excretion of salt. Restriction of water did not modify the rate of excretion of salt. A unilateral medullary lesion promoted the increased excretion of salt and water from both kidneys. Lastly, if the splanchnic nerve supply to the kidneys was interrupted bilaterally, a similar polyuria and saluresis were observed, and a puncture lesion in the medulla at this time did not produce any further change. They concluded that this lesion resulted in a specific effect on the renal tubular cells. Pick [39] refers to polyurias associated with cerebral lesions that are not responsive to the administration of antidiuretic hormone. Mehes and Molitor (discussed by Pick in his Harvey Lecture [39]) produced a polyuria with a lesion of the medial posterior thalamic region in the dog and rabbit which was unresponsive to antidiuretic hormone. Pötzl and Hoff (also discussed by Pick [39]) demonstrated that patients with lesions high in the cervical cord are unresponsive to antidiuretic hormone. Marshall and Kolls [40] studied the influence of renal denervation on the excretion of salt and water in the dog. They observed that the rate of excretion of water and salt was greater on the

39. Pick, E. P.: The Regulation of Water Metabolism, in the Harvey Lectures, 1928-1929, Baltimore, Williams & Wilkins Company, 1930.

40. Marshall, E. K., Jr., and Kolls, A. C.: Studies on the Nervous Control of the Kidneys in Relation to Diuresis and Urinary Secretion: I. The Effect of Unilateral Excision of the Adrenal, Section of the Splanchnic Nerve, and Section of the Renal Nerves on the Secretion of the Kidney, Am. J. Physiol. **49**:302, 1919.

denervated side. Since they were able to combat these effects [41] by compression of the renal artery, they concluded that the "denervation diuresis" was the result of hemodynamic changes. Nevertheless, there were no associated alterations in the rate of excretion of endogenous creatinine, so that it is unlikely that there had been a significant change in the rate of glomerular filtration. In another publication [42] these same authors compare the effects on the rates of excretion of water from the denervated and control kidney under the influence of infusions of hypertonic solutions of sodium chloride and sodium sulfate. When the chloride solution was infused, the difference in the rate of excretion of water in the two kidneys was marked. However, when the sulfate solution was infused, the denervated kidney had the same response, but the normal kidney achieved a diuresis of the same order of magnitude as its denervated companion. These observations are most compatible with the hypothesis that an interruption of the nerve supply to the kidneys does, in fact, alter proximal renal tubular activity in such a manner as to diminish the reabsorption of salt. Thus, when sodium chloride is infused, the urine flow from the denervated kidney is greater because a larger volume of proximal urine is delivered to the distal tubule as a consequence of the lessened reabsorption of salt. However, when the tubules are presented with sodium sulfate, a salt that neither the control nor the denervated nephron reabsorbs, the behavior of the normal and of the denervated kidney is the same. If the effect of the denervation were simply related to altered vascular dynamics, there should always be a distinct difference between the two sides. Kriss, Futcher, and Goldman [43] and, more recently, Kaplan and Rapaport [44] have reinvestigated this problem in the dog. The data from these studies, especially that of Kaplan and Rapaport, are quite convincing that denervation of the kidney modifies renal tubular activity. The latter authors conclude that the alteration is in the proximal tubule since the most striking and consistent results are found when the experiments are conducted in a hydropenic state and under the influence of an "osmotic diuresis" with sodium chloride.

A salt-wasting syndrome has been described in a group of patients with a variety of cerebral lesions.[45] The very nature of the cerebral disease, which was diffuse in each instance (diffuse encephalitis, severe cerebrovascular disease, and bulbar poliomyelitis) defied any attempt to analyze the site of the responsible lesion. The syndrome was characterized by an inability to eliminate salt from the urine, despite depressed concentrations of sodium and chloride in the serum. These patients

41. Marshall, E. K., Jr., and Kolls, A. C.: Studies on the Nervous Control of the Kidneys in Relation to Diuresis and Urinary Secretion: II. A Comparison of the Changes Caused by Unilateral Splanchnotomy with Those Caused by Unilateral Compression of the Renal Artery, Am. J. Physiol. **49**:317, 1919.

42. Marshall, E. K., Jr., and Kolls, A. C.: Studies on the Nervous Control of the Kidneys in Relation to Diuresis and Urinary Secretion: V. Chloride and Sulphate Diuresis After Unilateral Splanchnotomy, Am. J. Physiol. **49**:339, 1919.

43. Kriss, J. P.; Futcher, P. H., and Goldman, M. L.: Unilateral Adrenalectomy, Unilateral Splanchnic Nerve Resection, and Homolateral Renal Function, Am. J. Physiol. **154**: 220, 1948.

44. Kaplan, S. A., and Rapaport, S.: Urinary Excretion of Sodium and Chloride After Splanchnicotomy: Effect on the Proximal Tubule, Am. J. Physiol. **164**:175, 1951.

45. Peters, J. P.; Welt, L. G.; Sims, E. A. H.; Orloff, J., and Needham, J.: A Salt-Wasting Syndrome Associated with Cerebral Disease, Tr. A. Am. Physicians **63**:57, 1950.

presented the evidences of true salt depletion, characterized by the retention of nitrogen and decrease in blood pressure, and responded favorably to the administration of salt. Two alternative hypotheses were suggested to explain this disorder:

> The excitation of the anterior pituitary gland as this relates to the secretion of adrenocorticotrophic hormone may be under a modifying influence from some nucleus or tract in the central nervous system. A lesion at such a site might disorganize an automatic sequence that normally leads to the secretion of ACTH and in turn of salt retaining hormone from the adrenal cortex. Another explanation would have to be based on the premise that there is a direct nervous influence from the central nervous system to the kidney that can modify the tubular reabsorption of salt.[45]

Since those first cases were reported, several additional patients have been studied in an effort to gain some insight into the mechanism responsible for this disorder. The observations may allow the construction of a hypothesis concerning the nature of the physiologic defect in this syndrome.

The first of these patients, A. C. (A49605), was a 60-year-old woman admitted to the hospital on Jan. 26, 1951, with left-sided weakness of one week's duration. She had been bedridden during that week and had had no food and little water. The blood pressure on admission was 130/80, which was probably low for this patient, since readings later in her course were all consistently high. The pulse rate was 80. She was described as emaciated, dehydrated and somewhat somnolent and had sacral decubitus ulcers. There were evidences of arteriosclerosis and arteriolar sclerosis; the heart was enlarged, and the lungs were clear. There were facial weakness on the left, diminution in pain and touch sensations over the distribution of the left fifth cranial nerve, spastic paralysis of the left arm, and spasticity and weakness of the left leg. The plantar response was extensor on the left.

On admission the red blood cell count was 5,240,000 per cubic millimeter, and the hemoglobin concentration was 13.5 gm. per 100 cc. Urinalysis gave normal results except for a 1 + reaction for sugar and evidences of urinary tract infection. A low initial pressure was recorded during the lumbar puncture. Analysis of the blood and serum the following morning revealed a nonprotein nitrogen of 32 mg. per 100 cc. and sodium of 122.5 mEq., potassium of 4.0 mEq., bicarbonate of 26 mEq., and chloride of 82 mEq., per liter. She was treated with infusions of hypertonic and isotonic solutions of salt, and on Jan. 29 the nonprotein nitrogen was 22 mg. per 100 cc.; fasting blood sugar was 63 mg. per 100 cc., and sodium 129.4 mEq., potassium 3.9 mEq., bicarbonate 33 mEq., and chloride 89.5 mEq., per liter. The following day, when the concentration of sodium in the serum was still depressed, a casual urine was found to have a concentration of chloride of 106 mEq. per liter.

There was a decrease of 78% in the number of eosinophiles four hours after the administration of 0.3 mg. of epinephrine. A five-hour dextrose-tolerance test revealed no suggestion of a disorder in carbohydrate metabolism. The responses to the administration of desoxycorticosterone in a dose of 10 mg. a day and to corticotropin in a dose of 30 mg. administered at six-hour intervals are described in Figure 6. The administration of desoxycorticosterone promoted a positive balance of sodium of 61 mEq. per day, associated with an increase in the concentration of sodium in the serum. This retention seems slight in relation to the 308 mM. of salt made available. Despite this modest retention of salt, a distinct potassium depletion developed, as evidenced by the depressed concentration of this ion in the serum, 2.9 mEq. per liter, and the presence of a hypochloremic alkalosis. Discontinuance of desoxycorticosterone administration was accompanied with a negative balance of sodium and a decrease in its concentration in the serum. Potassium was retained; its concentration in the serum increased, and the bicarbonate concentration fell to normal levels.

The administration of corticotropin was accompanied with a positive balance of sodium in the first four days of the same order of magnitude observed after the administration of desoxycorticosterone. In the second four-day period of corticotropin administration, however, the balance of sodium became negative despite the fact that the same intake of salt obtained. Moreover, the negative balance of potassium was quite large, averaging 54 mEq. per day during the first four days, and in the second four days there was a small positive balance, but only

in the face of the administration of an average of 147 mEq. of potassium per day. Furthermore, when the corticotropin therapy was discontinued and the balance of sodium was more negative, there was no change in the average daily positive balance of potassium. Once again, a modest retention of salt was associated with the development of a striking depletion of potassium.

The second patient (R. T., A16057) was a 68-year-old man admitted to the hospital on Aug. 1, 1951, with the chief complaints of weakness and pain in the left leg of nine months' duration, vertigo and ataxic gait for six months, and paresthesia of the right foot and hand of one month's duration. A ventriculogram performed on Aug. 8 revealed a filling defect in the floor of the fourth ventricle. A craniotomy was performed on Aug. 13. There was an area of discoloration in the floor of the fourth ventricle about 8 mm. above the obex, and, when the lower portion of the vermis was transected, granular yellow-gray tumor tissue was seen. This tumor could not be removed *in toto*.

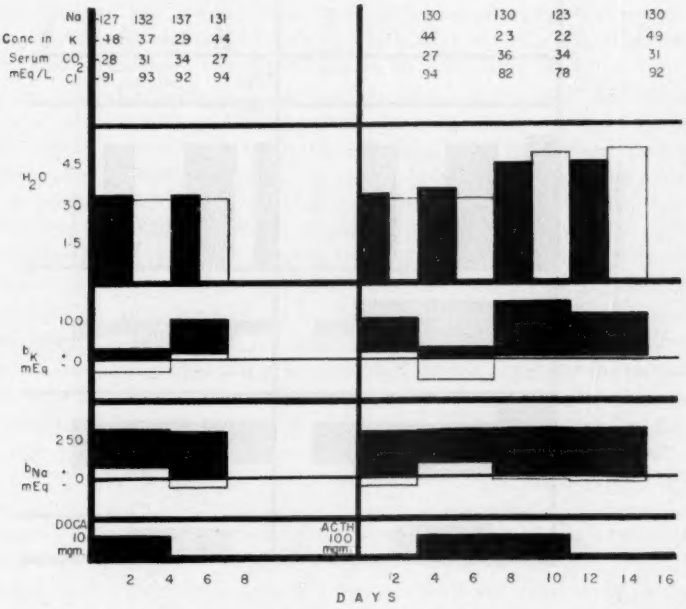

Fig. 6.—Responses to the administration of desoxycorticosterone acetate (DOCA) and corticotropin (ACTH) in patient with cerebral salt-wasting syndrome. Height of columns refers to intake (black) and output (white) with respect to water. Symbols b_K and b_{Na} refer to balances of potassium and sodium, respectively. Height of black columns next to these symbols represents intake of respective ion. Height of white columns represents external balance of respective ion: positive if above the line, and negative if below the line.

The immediate postoperative course was stormy, with a marked elevation of the blood pressure to 215/115 and very rapid respirations suggestive of diaphragmatic flutter. The clinical status improved, and blood pressure and respiratory activity were normal in 48 hours. At this time, Aug. 15, analysis of the patient's blood revealed a nonprotein nitrogen of 46 mg. per 100 cc., sodium of 114.5 mEq., potassium of 4.2 mEq., bicarbonate of 22.3 mEq., and chloride of 84.2 mEq., per liter. He received 70 gm. of salt in the next two days, and on Aug. 17 the nonprotein nitrogen was 39 mg. per 100 cc.; sodium was 135 mEq., potassium 4.6 mEq., bicarbonate 22.5 mEq., and chloride 105 mEq., per liter. Whenever he received as little as 9 gm. of salt a day, the concentration of sodium in the serum fell. On Aug. 25, the concentration of sodium in

the serum was 127 mEq. per liter and a casual urine contained 129 mEq. per liter of chloride. In the 24 hours from Sept. 1 to 2, the intake of salt was 9 gm. and 25 gm. was excreted in the urine.

The eosinopenic response to 0.3 mg. of epinephrine was examined on Sept. 8, and there was a decrease of 74% in four hours. The responses to the administration of desoxycorticosterone and corticotropin are represented in Figure 7. There was an increase in the total daily urinary excretion of 17-ketosteroids from 8.8 and 9.8 mg. to 38.3 and 42.6 mg. under the influence of corticotropin.

During the period of administration of 5 mg. of desoxycorticosterone per day there was an average daily positive balance of 81 mEq. of sodium in the face of a daily intake of 428 mEq. He then received 10 mg. of desoxycorticosterone a day for five days and showed an average

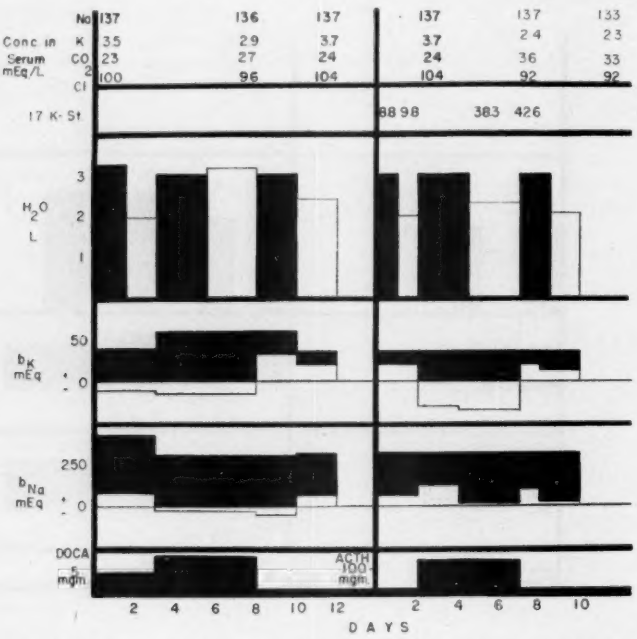

Fig. 7.—Responses to administration of desoxycorticosterone acetate (DOCA) and corticotropin (ACTH) in patient with cerebral salt-wasting syndrome. Symbols are explained in legend to Figure 6.

daily negative balance of 20 mEq. of sodium on an intake of 308 mEq. per day. Despite this change in balance of sodium, there was a persistently negative balance of potassium throughout the entire period of administration of desoxycorticosterone. As in the former case a distinct potassium deficiency developed, which was corrected when the use of desoxycorticosterone was discontinued. The positive and negative balances of sodium were correlated with positive and negative balances of water.

During the first two days of the administration of corticotropin the average daily positive balance of sodium increased to 125 mEq.; but in the next three days this fell to an average of 9 mEq. Despite the marked decrease in the positive balance of sodium during the administration of corticotropin, the negative balance of potassium persisted and, if anything, became more negative. Once again there were evidences of a deficiency of potassium. When corticotropin administration was discontinued, potassium was retained.

These observations allow some conclusions and provoke certain speculations concerning the defect responsible for the cerebral salt-wasting syndrome.

So far as the eosinopenic response to epinephrine is a valid indicator of secretion of corticotropin by the anterior pituitary gland and a response to corticotropin on the part of the adrenal cortex, both these patients appeared to have a normal pituitary-adrenal axis. The marked increase in the total daily excretion of 17-ketosteroids in response to the administration of corticotropin leaves little doubt concerning the ability of the adrenal cortex to respond in this respect to stimulation by corticotropin. With this evidence at hand it would appear unlikely that a defect in either anterior pituitary or adrenal cortical response was responsible for the disorder.

Both patients had striking deficiencies of potassium under the influence of desoxycorticosterone and corticotropin with little relation to the magnitude, or even direction, of the influence of these substances on the balance of sodium.

It has been clearly demonstrated both in man and the rat [46] that prolonged periods of injection of large doses of desoxycorticosterone or corticotropin do not promote any increase in the daily excretion of potassium if the subjects are kept on a regimen with minimal salt intake. In other words, these preparations appear to have no primary effect on the metabolism of potassium. Its augmented excretion is conditioned by the effect of these compounds in promoting an increased reabsorption of sodium when this ion is available in the diet. Therefore, the fact that there was a striking negative balance of potassium in these patients must mean that the (distal) tubular reabsorption of salt had been increased. Despite this, the over-all positive balance of sodium was not large and was even negative in some periods. These data can be explained if it is assumed that the primary defect in cerebral salt wasting is an inability on the part of the proximal tubules to reabsorb salt properly. As a consequence large amounts of salt and water are delivered to the distal tubules. This large quantity of distal tubular salt may not be completely reabsorbed, even under the influence of desoxycorticosterone or corticotropin, and a certain amount escapes into the urine. Since an initial retention of salt under the influence of the administered hormones would result in the subsequent rejection of a larger fraction of filtered salt by the proximal tubule, even more would be delivered to the distal tubule and thus set the stage for a greater loss into the urine. This would be similar to the observation that the increased excretion of salt by the experimentally denervated kidney is more dramatically demonstrated when hypertonic saline solutions are administered. If this hypothesis were valid, these patients could be said to be undergoing a constant so-called osmotic diuresis, which would explain the large flows of dilute urine. This, of course, is only a hypothesis, and its validity must be tested by further investigation.

The site of the tumor in the last patient and the site of the medullary lesion that is said to produce experimental salt wasting are amazingly close.

This discussion has not concerned itself with the influence of the central nervous system on renal hemodynamics. This is not meant to imply that they may not be important determinants of the rates of excretion of salt and water in a variety of

46. Seldin, D. W.; Welt, L. G., and Cort, J. H.: The Effect of Pituitary and Adrenal Hormones on the Metabolism and Excretion of Potassium, J. Clin. Invest. **30**:673, 1951.

circumstances. In addition, no attention has been given to the influence of disordered respiratory activity secondary to lesions involving the medullary respiratory center, which may affect the metabolism and excretion of water and electrolytes by virtue of distortions in the acid-base pattern of the body fluids. No consideration has been given to the responses of the central nervous system to alterations in the tonicity of the body fluids in terms of specific cerebral functions, such as acuity of cerebration, state of consciousness, and alterations in seizure thresholds.[47]

This discussion has been an attempt to provide some insights into the contributions of the central nervous system to the well-ordered and integrated pattern of response with respect to the preservation of a few of the dimensions of the internal environment. A disorder of any one of these mechanisms may promote the development of gross distortions that must be classified as metabolic crises. The commonest of these disorders, the loss of consciousness, places the problems of fluid balance completely at the mercy of the physician. The simple failure to provide an appropriate amount of water or salt may readily jeopardize the ultimate recovery from an illness of which the loss of consciousness is only one of the symptoms.

An awareness of the potentialities for disorders in the metabolism and excretion of electrolytes and water in association with a variety of primary intracranial abnormalities will increase the frequency of their recognition and provide insights into the mechanisms involved. This must ultimately promote better care for the patient.

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47. Davenport, V. D.: Relation Between Brain and Plasma Electrolytes and Electro-Shock Seizure Thresholds in Adrenalectomized Rats, Am. J. Physiol. **156**:322, 1949. Woodbury, D. M., and Davenport, V. D.: Brain and Plasma Cations and Seizures in Normal and Desoxycorticosterone Treated Rats, ibid. **157**:234, 1949.

TREATMENT OF POLYCYTHEMIA VERA WITH TRIETHYLENE MELAMINE

Summary of Thirty Cases

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THE PURPOSE of this paper is to present data on the treatment of polycythemia vera with triethylene melamine (T. E. M.), based on the study of 30 cases followed for an average period of more than one year. Triethylene melamine, a compound which has nitrogen-mustard-like action, has the advantage that it is effective upon oral administration. The development of triethylene melamine, its pharmacological properties, and its use in patients with lymphomas, leukemia, and various carcinomas have been extensively discussed in papers by Karnofsky and associates [1] and Wright and co-workers.[2] Because of its ease of administration and its depressant effects upon hematopoiesis, which appear to resemble those of nitrogen mustard (methyl-*bis* or *tris* [β-choroethyl] amine hydrochloride) and x-irradiation,[3] it appeared that triethylene melamine might be of value in the treatment of polycythemia vera.

Emphasis upon the treatment of polycythemia by bone marrow inhibition is largely derived from the work of Lawrence,[4] who originated the use of radioactive phosphorus, which may sometimes produce remissions of up to a few years following a single injection. In addition to lowering the red blood cell count, marrow inhibition causes a reduction in the number of thrombocytes (platelets), which are

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This work was performed on ambulatory patients in the hematological laboratory and practice of Dr. N. Rosenthal.

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1. Karnofsky, D. A.; Burchenal, J. H.; Armistead, G. C.; Southam, C. M.; Bernstein, J. L.; Craver, L. F., and Rhoads, C. P.: Triethylene Melamine in the Treatment of Neoplastic Disease, A. M. A. Arch. Int. Med. **87**:477-516 (April) 1951.

2. Wright, J. C.; Prigot, A.; Wright, L. T., and Arons, I.: Further Observations on the Use of Triethylene Melamine in Neoplastic Diseases, A. M. A. Arch. Int. Med. **89**:387-404 (March) 1952.

3. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the β-Chloroethyl Amines and Sulfides, Science **103**:409-415 (April 5) 1946. Rhoads, C. P.: Nitrogen Mustards in the Treatment of Neoplastic Disease: Official Statement, J. A. M. A. **131**:656-658 (June 22) 1946. Goodman, L. S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy, ibid. **132**:126-132 (Sept. 21) 1946. Jacobson, L. O.; Spurr, C. L.; Barron, E. S. G.; Smith, T.; Lushbaugh, C., and Dick, G. F.: Nitrogen Mustard Therapy, ibid. **132**:263-271 (Oct. 5) 1946.

4. Lawrence, J. H.: The Control of Polycythemia by Marrow Inhibition, J. A. M. A. **141**:13-18 (Sept. 3) 1949.

elevated in more than 50% of the cases of polycythemia vera.[5] Thrombocythemia contributes to both hypercoagulability and abnormal clot formation and retraction, which, aggravated by the presence of an elevated hematocrit percentage, may lead to either intravascular thrombosis or hemorrhage.[6] These serious complications are markedly reduced after therapy with radioactive phosphorus. Other marrow-depressing agents, such as urethan[7] and nitrogen mustard,[8] have been used with none or with less striking effect. Recently, an aromatic nitrogen mustard compound, β-naphthyl-di-2-choroethylamine (R 48), for oral administration was found to produce remissions in five of six patients with polycythemia vera by Meulengracht and his co-workers.[9] This medicament was taken in dosage of 100 mg. two to six times a day for two to four months in order to produce an effect.

PROCEDURE OF STUDY

Material.—The 30 patients included in this study have had polycythemia vera for 1 to 20 years. Seven patients have had no therapy other than phlebotomy, while the remainder have previously been treated with radioactive phosphorus, urethan, potassium arsenite solution (Fowler's solution), x-rays, or phenylhydrazine. In this study, phlebotomy was withheld for at least one month prior to the beginning of triethylene melamine therapy, and after therapy until the therapeutic effect was apparent. Patients were followed and blood studies performed at two- to four-week intervals. Blood studies included red cell, thrombocyte, white cell, and differential counts and hemoglobin and hematocrit determinations. Reticulocyte counts and bone marrow aspiration were occasionally performed.

Dosage.—Triethylene melamine was taken orally one hour before breakfast in dosage of 2.5 or 5 mg. every one to three days, reaching a total dose of 15 to 40 mg. Additional dosage was given two to three months later, depending upon the hematological response. There were generally no untoward effects of the drug except for an occasional complaint of nausea.

RESULTS

The patients are divided into three groups according to their response to triethylene melamine: Group I, red blood cell count and hematocrit percentage reduced to normal levels; Group II, red blood cell count and hematocrit percentage reduced to values slightly above normal, and Group III, little or no response. A summary of the results is presented in Table 1. Twenty of the 30 patients (Groups I and II) showed a satisfactory response to triethylene melamine, with an average remission of eight to nine months. Eight patients are in remission up to the present. Further analysis revealed that the average age of the patients in Group III was higher than that of those in Groups I and II. The mean duration of disease from the time of laboratory diagnosis to onset of therapy was the shortest in Group I. Five patients in Group I and two patients in Group III had received no previous therapy other than phlebotomy.

5. Rosenthal, N., and Bassen, F. A.: Course of Polycythemia, Arch. Int. Med. **62**:903-917 (Dec.) 1938. Lawrence.[4]

6. Rosenthal, R. L.: Blood Coagulation in Leucemia and Polycythemia: Value of the Heparin Clotting Time and Clot Retraction Rate, J. Lab. & Clin. Med. **34**:1321-1335 (Oct.) 1949.

7. Rosenthal, N.: Unpublished data.

8. Spurr, C. L.; Smith, T. R.; Block, M. H., and Jacobson, L. O.: A Clinical Study of the Use of Nitrogen Mustard Therapy in Polycythemia Vera, J. Lab. & Clin. Med. **35**:252-264 (Feb.) 1950.

9. Iverson, K., and Meulengracht, E.: Oral Treatment of Polycythaemia Vera with β-Naphthyl-di-2-Chloroethylamine, Brit. M. J. **2**:510 (Sept. 1) 1951.

From the standpoint of dosage, the patients in Groups I and II generally received one course averaging 30 to 35 mg., while the patients in Group III received an average of 59 mg., given in multiple courses because of their poor response.

TABLE 1.—*Summary of Results of Treatment of Polycythemia Vera with Triethylene Melamine*

	Group I*	Group II†	Group III‡
No. of patients	12	8	10
Male	6	5	3
Female	6	3	7
Average age, yr.	56	53	61
Duration of disease from laboratory diagnosis, yr.	4.0	6.5	5.3
Average dose of triethylene melamine, mg.	31.5	37.0	59.0
Follow-up, mo.	12	13	11
Remission, mo.	9	8	1
No. of patients in remission to present	6	2	0

* Red blood cell count and hematocrit percentage reduced to normal levels.
† Red blood cell count and hematocrit percentages reduced to values slightly above normal.
‡ Little or no response.

TABLE 2.—*Changes in Erythrocytes, Hemoglobin Concentration, Hematocrit Percentage, White Blood Cells, and Thrombocytes After Triethylene Melamine Therapy*

	Group I	Group II	Group III
No. of patients	12	8	10
Erythrocytes, × 10 ⁶			
Before T. E. M.	8.0	7.1	7.9
Lowest value after T. E. M.	4.4	5.6	6.8
Time reached, mo.	5	3	4
% decrease	45	21	13
Hemoglobin, gm./100 cc.			
Before T. E. M.	17.2	15.1	14.8
Lowest value after T. E. M.	12.0	13.2	14.3
Time reached, mo.	4	4	3
% decrease	30	13	4
Hematocrit, %			
Before T. E. M.	64	55	61
Lowest value after T. E. M.	41	49	57
Time reached, mo.	4	3	2
% decrease	36	10	7
White blood cells			
Before T. E. M.	19,140	14,790	24,500
Lowest value after T. E. M.	4,620	8,150	10,560
Time reached, mo.	2	2	5
% decrease	76	45	57
Elevated W. B. C. before T. E. M.	7 (58%)	3 (37%)	10 (100%)
Thrombocytes			
Before T. E. M.	400,000	370,000	600,000
Lowest value after T. E. M.	110,000	170,000	260,000
Time reached, mo.	2	2	3
% decrease	72	54	56
Elevated thrombocytes before T. E. M. (no. of patients)	4 (33%)	2 (25%)	7 (70%)
Spleen palpable before therapy (no. of patients)	2 (16%)	6 (75%)	6 (60%)

Hematological Response.—Table 2 presents an analysis of the hematological changes following triethylene melamine therapy. The changes in the red blood cells, hemoglobin concentration, and hematocrit percentage are compatible with the above-described classification of the patients in the three groups. The lowest erythrocyte, hemoglobin, and hematocrit levels were reached in an average of four months after therapy. The erythrocytes generally showed a greater percentage

decrease than did the hemoglobin and the hematocrit levels. The white blood cell and thrombocyte counts are interesting. All the patients in Group III, as compared with 50% of patients in Groups I and II, had elevated white blood cell counts before therapy. Patients in Group I showed the greatest percentage drop in white blood cells, which was 76% at two months after therapy, as compared with 45 and 57% in Groups II and III, respectively. Since the patients studied generally had a shift to the left and a relative lymphopenia, the white blood cell changes reflect chiefly the changes in granulocytes.

Seventy per cent of the patients in Group III, as opposed to 30% of those in Groups I and II, showed elevated thrombocyte counts before therapy. The maximal decreases of the thrombocytes and their time relationships after therapy were similar to the changes in the white blood cells for each of the three groups. Prior to therapy, the spleen was palpable in 60% of the patients in Group III and in 40% of those in Groups I and II.

After reaching their minimum value, the thrombocytes and white blood cells gradually increased but appeared to remain below pretreatment levels for nine months or more, depending upon the duration of remission. In general, patients in Group I showed the most marked depression of red blood cells, white blood cells, and thrombocytes. The patients in Group II, as compared with those in Group III, showed greater depression of the red blood cells and about the same degree of depression of white blood cells and thrombocytes. However, these findings must be evaluated in view of the higher mean dose received by the patients in Group III.

Symptomatic Response.—In general, symptoms disappeared as the red blood cell count and hematocrit percentage fell after therapy. After remission, when the red blood cells increased, symptoms generally reappeared but sometimes lagged behind the rise in red blood cell count. In patients of Group III, in whom no change in the red blood cell count occurred, there was no symptomatic response to therapy. In this analysis, it is important to emphasize the variability and subjectivity of symptoms in polycythemia vera.

Individual Cases.—Table 3 summarizes the clinical and hematological data on the patients included in this study. Figures 1, 2, 3, and 4 present examples of the hematological responses to triethylene melamine of patients in Group I. Abstracts of some illustrative cases are herewith presented.

ABSTRACTS OF CASES

Group I.—Red blood cells and hematocrit percentages reduced to normal levels.

CASE 1.—S. W., 56 years old, had a myocardial infarction five years ago and complained of dizziness for three years. Two years ago, he had thrombophlebitis and a pulmonary embolism. A few months later, a diagnosis of polycythemia vera was made; the spleen and liver were not palpable. He was treated initially by intermittent phlebotomy with some relief from symptoms, but his hemoglobin concentration showed a marked drop to 13.6 gm. per 100 cc., with a red blood cell count of 9,800,000. In April, 1950, he received 5 mc. of P^{32}. The minimum red blood cell count of 6,880,000 and hematocrit reading of 50% were recorded three months later. Therapy with triethylene melamine (35 mg. total) was started in December, 1950, at which time he complained of headaches and dizziness. For 13 months (to February, 1952) the patient has been in remission, both hematologically and symptomatically, and has required no other therapy. Results of blood studies are listed in Table 4.

TABLE 3.—*Clinical and Hematological Data on Polycythemic Patients Treated with Triethylene Melamine*

Case No.; Age, Yr.; Sex	Duration,† Yr.	Previous Therapy‡	T. E. M. Dose, Mg.	T. E. M. No. Courses	Follow-Up, Mo.	Remission, Mo.	Before T. E. M. R. B. C., × 10⁶	Before T. E. M. Hgb., Gm./100 Cc.	Before T. E. M. Hematocrit, %	Before T. E. M. W. B. C.	Before T. E. M. Thrombocytes, × 10³	Lowest Values After T. E. M.* R. B. C., × 10⁶	Lowest Values After T. E. M.* Hgb., Gm./100 Cc.	Lowest Values After T. E. M.* Hematocrit, %	Lowest Values After T. E. M.* W. B. C.	Lowest Values After T. E. M.* Thrombocytes, × 10³
GROUP I																
1; 56; M	2	Ph., P^{32}	35	1	13	13	7.8	16.8	59	7,500	200	4.3 (3)	10.6 (3)	38 (2)	2,750 (1)	70 (1)
2; 62; F	1	0	20	1	12	12	9.7	22.0	80	7,200	290	3.7 (5)	11.0 (4)	35 (5)	2,800 (3)	40 (3)
3; 52; M	2	Ph.	40	1	12	12	7.8	12.2	52	9,150	370	4.4 (6)	9.4 (3)	33 (3)	4,150 (1)	40 (1)
4; 66; F	4	As_2O_3, P^{32}	35	1	13	10	7.2	15.0	59	15,800	130	3.6 (4)	10.8 (4)	38 (5)	4,200 (4)	30 (2)
5; 50; M	11	P^{32}	20	1	10	10	7.5	16.9	58	13,250	500	3.9 (6)	11.2 (4)	40 (6)	4,050 (2)	130 (2)
6; 58; F	5	Ph.	40	1	9	9	8.0	17.0	66	11,200	610	4.5 (9)	12.5 (7)	43 (7)	3,200 (2)	180 (9)
7; 59; F	1	0	20	1	17	9	10.7	20.2	76	8,850	150	3.2 (4)	8.6 (3)	33 (3)	1,350 (2)	20 (2)
8; 60; M	1	Ph.	30	1	14	2	7.9	16.2	70	81,000	570	6.3 (3)	16.0 (2)	55 (3)	5,450 (3)	250 (3)
			20	1	..	9	8.1	18.5	64	16,000	400	4.2 (5)	11.0 (5)	47 (5)	4,300 (2)	90 (2)
9; 44; M	4	Ph., P^{32}	30	1	11	8	7.3	20.5	67	15,750	150	4.8 (5)	16.0 (5)	47 (8)	6,150 (2)	140 (1)
10; 56; F	7	P^{32}	20	1	7	7	7.1	18.5	63	11,150	260	5.1 (3)	13.4 (3)	41 (3)	8,700 (1)	60 (1)
11; 53; M	6	Ph., As_2O_3, ure., P^{32}	40	1	16	7	9.0	17.0	69	28,000	260	4.7 (5)	13.8 (5)	45 (5)	4,950 (3)	150 (3)
12; 56; F	5	P^{32}	30	1	13	6	6.5	13.0	48	25,000	1,290	4.8 (5)	13.0 (3)	44 (1)	8,000 (5)	250 (1)
GROUP II																
13; 46; F	5	Ph., X, P^{32}	..	1	14	14	7.0	12.0	52	15,900	230	5.9 (1)	12.2 (7)	44 (1)	4,150 (1)	70 (1)
14; 61; M	7	Ph., P^{32}	15	1	12	12	6.6	16.0	54	6,950	120	5.8 (5)	15.2 (8)	52 (7)	5,450 (4)	150 (5)
15; 46; F	7	Ph., X	25	1	12	7	5.9	13.5	48	6,800	180	5.7 (2)	11.8 (1)	47 (1)	5,900 (2)	110 (4)
16; 60; M	3	P^{32}	20	1	12	6	5.9	14.0	49	20,200	690	4.9 (1)	14.0 (3)	47 (1)	1,400 (1)	250 (1)
17; 41; M	6	Ph., P^{32}	55	1	13	6	8.6	20.0	63	7,900	150	5.9 (5)	14.0 (5)	55 (5)	5,750 (2)	70 (2)
18; 56; M	2	Ph., P^{32}	65	3	14	6	6.1	12.0	51	42,000	1,000	5.7 (1)	10.4 (3)	48 (3)	32,000 (1)	410 (1)
19; 58; M	5	Ph., P^{32}	20	1	10	5	8.4	19.5	66	10,200	250	6.1 (3)	15.0 (1)	50 (3)	7,800 (1)	180 (1)
20; 53; F	17	Ph., phen., X	20	2	13	5	8.7	13.8	57	8,400	330	5.2 (3)	13.2 (3)	47 (3)	2,750 (1)	130 (1)
GROUP III																
21; 61; M	2	Ph.	40	2	12	7	7.0	13.2	50	15,650	1,190	6.2 (5)	12.0 (4)	50 (4)	13,200 (2)	460 (1)
22; 67; F	10	Ph., P^{32}	75	..	11	4	8.4	10.8	55	47,000	440	5.3 (2)	11.5 (1)	47 (1)	8,650 (2)	100 (1)
23; 55; M	1	As_2O_3	25	..	8	2	8.3	16.0	63	30,000	450	7.2 (2)	14.1 (1)	58 (1)	13,500 (2)	180 (3)
24; 64; F	4	Ph., P^{32}	50	..	13	..	8.3	12.8	56	28,000	720	5.6 (9)	15.6 (9)	54 (7)	9,250 (9)	240 (1)
25; 58; F	3	Ph., P^{32}	25	..	11	..	7.9	18.8	72	12,950	150	7.5 (1)	12.4 (1)	62 (2)	9,600 (4)	150 (2)
26; 67; F	1	0	120	..	7	..	7.2	16.8	64	20,550	1,070	6.9 (7)	17.5 (1)	59 (2)	1,175 (7)	450 (7)
27; 67; M	7	Ph., P^{32}	60	..	11	..	8.2	13.4	54	13,500	590	7.3 (4)	12.0 (9)	55 (2)	8,400 (4)	350 (5)
28; 48; F	3	P^{32}	55	..	13	..	9.2	17.0	69	15,950	630	8.0 (4)	17.8 (1)	66 (1)	10,450 (8)	260 (8)
29; 50; F	7	Ph., As_2O_3, phen., P^{32}	100	..	14	..	9.0	14.6	63	37,000	150	7.5 (1)	16.0 (2)	60 (2)	14,800 (3)	120 (2)
30; 66; F	15	Ph., P^{32}, ure.	40	..	6	..	5.8	11.0	43	27,000	300	3.4 (1)	7.4 (1)	29 (1)	4,550 (1)	120 (1)

* Values in parentheses represent time in months after triethylene melamine therapy.
† Duration of disease from time of laboratory diagnosis.
‡ Ph. indicates phlebotomy; As_2O_3, potassium arsenite solution; X, x-rays; ure., urethan; phen., phenylhydrazine.

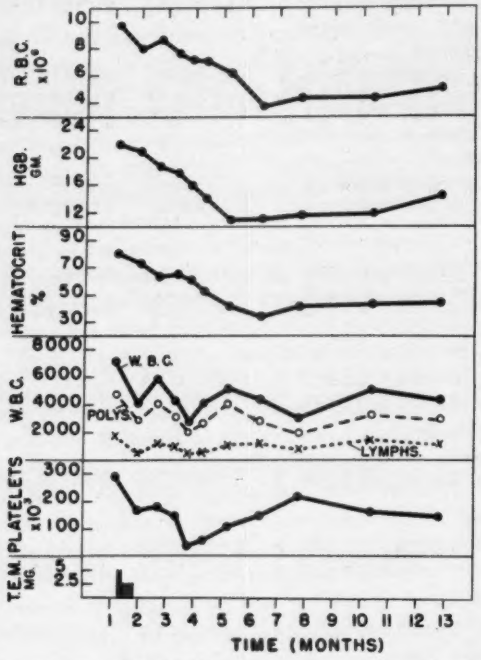

Fig. 1 (Case 2).—Hematological changes after triethylene melamine therapy.

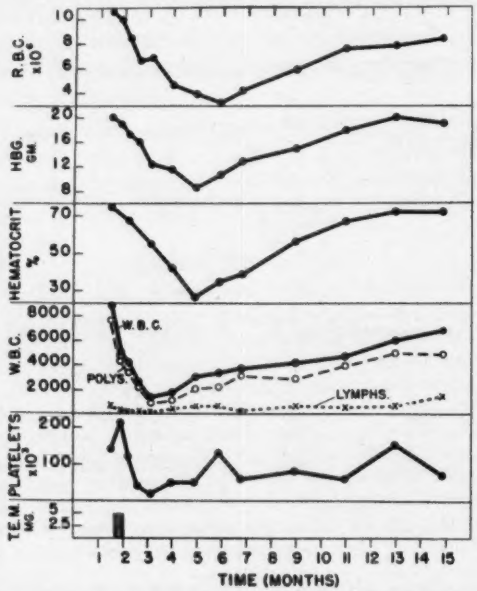

Fig. 2 (Case 7).—Hematological changes after triethylene melamine therapy.

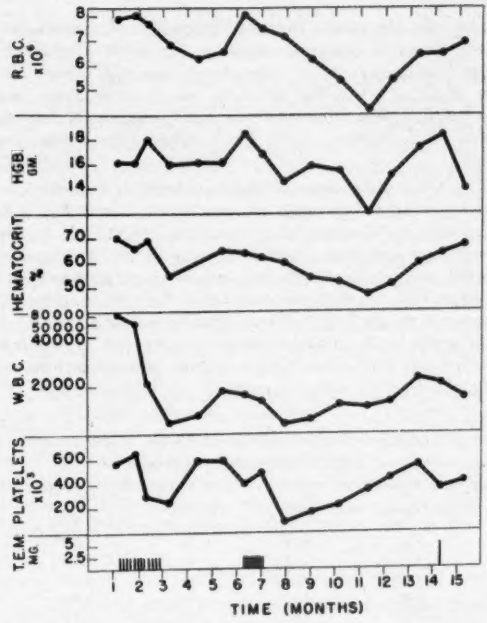

Fig. 3 (Case 8).—Hematological changes after triethylene melamine therapy.

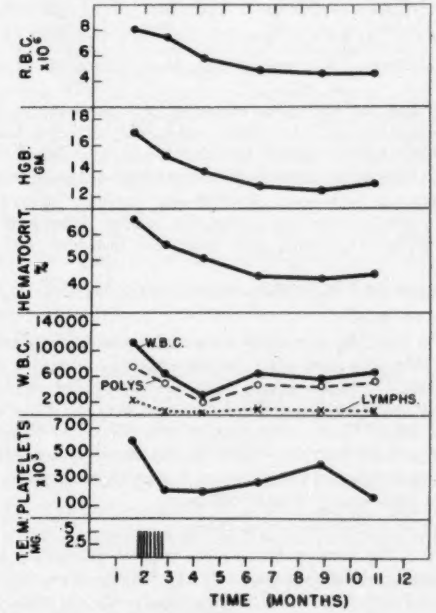

Fig. 4 (Case 6).—Hematological changes after triethylene melamine therapy.

CASE 2.—L. T., 62 years old, gave a five-year history of headaches, dizziness, and bloodshot eyes and a three-week history of weakness and pain in her hands. She stated that she "bleeds" easily. In December, 1950, a diagnosis of polycythemia vera was made (Table 3 shows initial blood picture), and 20 mg. of triethylene melamine was given in divided doses over a 14-day period. The patient has now been in symptomatic and hematological remission for 12 months and has required no other therapy. Serial blood values after treatment are presented in Figure 1.

CASE 7.—R. O., a 59-year-old woman, presented a history of hypertension since 1941 and of more recent chest pains, occasional dizziness, and hoarseness. Hematological findings in August, 1950, were consistent with the diagnosis of polycythemia vera (Table 3), and the patient was given 20 mg. of triethylene melamine over an eight-day period. The spleen was not palpable. As shown in Figure 2, the red blood cells and hematocrit percentage began to show definite decreases without phlebotomy less than one month after the start of therapy. At one and a half months, the thrombocytes dropped to 20,000, and the patient displayed a mild purpura which disappeared in a few weeks as the thrombocyte count began to rise. The remission lasted nine months, and the patient has been given further therapy with triethylene melamine. It is too soon to evaluate the results of the second course.

TABLE 4.—*Hematological Studies on Patient S. W. (Case 1) After Treatment with Triethylene Melamine* *

Date	R. B. C., × 10 ⁶	Hgb., Gm./100 Cc.	Hematocrit, %	W. B. C.	Thrombocytes
12/27/50	7.81	16.8	59	7,500	200,000
1/17/51	6.57	14.5	41	2,750	70,000
2/19/51	4.98	11.0	38	3,050	90,000
3/27/51	4.32	10.6	40	6,950	190,000
5/ 7/51	5.47	15.7	..	8,600	190,000
6/18/51	5.01	15.2	50	5,400	140,000
7/31/51	5.31	14.7	50	7,100	190,000
10/ 3/51	5.16	14.3	48	7,100	160,000
12/10/51	5.69	14.5	48	6,950	200,000
2/20/52	5.04	13.2	52	9,000	220,000

* Patient received 35 mg. of triethylene melamine from Dec. 27, 1950, to Jan. 17, 1951.

CASE 8.—S. S., 60 years old, had severe abdominal pain and vomiting in May, 1950. Blood studies indicated polycythemia vera. The spleen, tremendously enlarged down to the pelvis, was removed because of symptoms of bowel obstruction and displacement of the kidneys. In November, 1950, the patient was given 30 mg. of triethylene melamine over a six-week period, and, as shown in Figure 3, a remission of three months' duration occurred. A second course of 20 mg. was followed by another remission lasting nine months. Subsequently, he has apparently developed resistance to further therapy with triethylene melamine, and treatment with P^{32} has been begun.

Group II.—Red blood cells and hematocrit percentages reduced to levels slightly above normal.

CASE 13.—M. K., 46 years old, was found to have polycythemia vera and enlargement of the spleen to the pelvis in 1946. For many years she was subject to headaches, intermittent dizziness, red hands, and pruritus. Up to November, 1950, the patient had received P^{32}, intermittent phlebotomies, and x-ray therapy to the spleen, but the red blood cells and hematocrit percentage had never dropped to normal levels. After therapy with triethylene melamine, the patient has shown symptomatic improvement and the spleen has decreased in size. Although the red blood cells and hematocrit percentage have not decreased to normal levels, the disease has been under control and the patient has required no other therapy.

Group III.—No response to triethylene melamine.

CASE 29.—E. L. was found to have polycythemia vera seven years ago. She had intermittent headaches and insomnia. Her previous therapy has included phlebotomy and administration of potassium arsenite solution, phenylhydrazine, and P^{32}, but she never had a true hematological

remission. From August, 1950, to March, 1951, the patient received a total of 100 mg. of triethylene melamine with no definite effect on any of the blood elements.

CASE 30.—R. W. died of terminal leukemia six months after therapy with triethylene melamine. She was a 66-year-old woman who gave a history of dizzy spells, headaches, nausea, and a sensation of falling, dating back 18 years. In 1936, the diagnosis of polycythemia vera was made and the red blood cell count was reported to be as high as 12,000,000. Phenylhydrazine was given. In 1946, the blood count revealed 7,450,000 red cells, a hemoglobin concentration of 14.6 gm. per 100 cc., a hematocrit reading of 54%, 310,000 thrombocytes, and 29,900 white cells, with 8% myelocytes, 28% band neutrophiles, 44% segmented neutrophiles, 2% eosinophiles, 2% basophiles, 8% lymphocytes, and 8% monocytes. Bone marrow examination in 1946 revealed 4% myeloblasts, 4% promyelocytes, 27.3% myelocytes, 7% metamyelocytes, 19.0% band neutrophiles, 11.3% segmented neutrophiles, 0.6% eosinophiles, 0.3% basophiles, 1.3% lymphocytes, 0.7% hematogones, 4.4% erythroblasts, and 20.0% normoblasts. The bone marrow showed excessive cellularity. From January, 1946, to December, 1949, the patient achieved some symptomatic relief after administration of 10 mc. of P^{32}, brief courses of urethan and cortisone, one course of x-ray therapy over the spleen, and one phlebotomy.

In January, 1951, the patient was very weak and the blood count revealed 5,800,000 red cells, 300,000 thrombocytes, and 27,000 white cells, with 13% myelocytes, 3% metamyelocytes, 16% band neutrophiles, 57% segmented neutrophiles, 2% basophiles, 7% lymphocytes, and 2% monocytes. Red blood cells revealed marked anisocytosis and poikilocytosis; elliptical red cells, as are seen in the late stage of polycythemia, were noted. The patient was given 40 mg. of triethylene melamine from Jan. 19 to March 20. Her course was progressively downhill, with the development of anemia and terminal hematemesis. She died in July, 1951.

COMMENT

This study indicates that triethylene melamine has good potentialities in the treatment of polycythemia vera. Longer follow-up is necessary before its value can be compared with that of radioactive phosphorus and its ultimate effects upon the course of the disease can be ascertained. Triethylene melamine may be useful in cases of resistance to radioactive phosphorus and vice versa. It offers the advantages of being generally available and easily administered by mouth.

The reason for the lack of response of some patients with polycythemia vera to marrow-inhibiting agents is not known. The present study indicates that older patients with a longer duration of disease and elevated white blood cell and thrombocyte counts are less likely to respond to triethylene melamine. Patients with brief duration of the disease, minimal previous therapy, and normal white blood cell and thrombocyte counts appear to respond better to triethylene melamine. It is, therefore, important to consider the stage and duration of the disease in polycythemia vera in the evaluation of therapeutic agents and measures. Lawrence and Rosenthal [10] reported on a patient resistant to P^{32} therapy who was subsequently found to have had myeloma in addition to polycythemia.

The analysis of the responses of the white blood cells and thrombocytes, as well as of the erythrocytes, provides a more complete picture of the effect of triethylene melamine on the bone marrow. Patients in Group I showed a relatively marked maximal diminution in red blood cells (45% decreased), white blood cells (76%), and thrombocytes (72%), while patients in Group II revealed moderate diminutions in the three elements: erythrocytes down 21%, white blood cells, 45%, and thrombocytes, 54%. This would indicate that the difference in erythrocyte response between

10. Lawrence, J. H., and Rosenthal, R. L.: Multiple Myeloma Associated with Polycythemia, Am. J. M. Sc. **218**:149-154 (Aug.) 1949.

the two groups can be attributed to less over-all depression of the bone marrow in Group II. In Group III, it not only required a higher dosage of triethylene melamine to produce a white blood cell and thrombocyte response similar to that in Group II, but there was a relative lack of erythrocyte response. This may indicate that in Group III patients, the erythrocytes and, to less degree, the white blood cells and thrombocytes were particularly resistant to triethylene melamine. It is also important to mention that the degree of changes in erythrocytes, white blood cells, and thrombocytes, as well as the duration of remission and the clinical response, indicated little relation to the amount of triethylene melamine given in a single course, over a range of 15 to 65 mg.

From the standpoint of toxicity, triethylene melamine is similar to any other marrow depressant. The patient must be closely followed hematologically. One episode of transient purpura occurred coincidentally with thrombocytopenia (20,000 cells). The thrombocyte count fell below 100,000 in 9 of 20 patients in Groups I and II after triethylene melamine therapy. This thrombocyte-depressant effect of triethylene melamine, as well as that of P^{32}, is important in the care of patients with thrombocythemia. The significance of this finding in relation to clot formation, hemorrhage, and thromboembolism has been previously discussed.[11] Although triethylene melamine did not produce significant changes in the red blood cell values of patients in Group III, it did effect a definite decrease in thrombocytes in all the seven patients with counts above 400,000.

SUMMARY

Thirty patients having polycythemia vera were treated with triethylene melamine. Twenty patients showed a satisfactory symptomatic and hematological response, with an average remission of eight to nine months following an average course of 30 mg. of triethylene melamine. Analysis of these cases revealed that patients with a shorter duration of disease and normal thrombocyte and white blood cell counts responded more favorably to treatment than did patients with a long history of the disease and elevated white blood cell and thrombocyte counts. The additional value of triethylene melamine as a depressant of elevated thrombocyte counts is discussed in relation to thromboembolic and hemorrhagic complications.

This study indicates that triethylene melamine offers good potentialities in the treatment of polycythemia vera. Further observation is necessary before valid comparisons with P^{32} therapy can be made.

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Dr. J. M. Ruegsegger, of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., provided the triethylene melamine, and Meryl Rosenthal assisted in compiling the data.

11. Lawrence.[4] Rosenthal.[6]

MANDIBULAR JOINT NEURALGIA (COSTEN'S SYNDROME)

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MANDIBULAR joint neuralgia (Costen's syndrome), first reported by Costen in 1934,[1] is accepted by otorhinolaryngologists and members of the dental profession as a definite clinical entity. It should be considered in every differential diagnosis of recurring facial pain. Nevertheless, the literature usually perused by the internist contains very few references to this syndrome of vertex and occipital pain, otalgia, glossodynia, and pain about the nose and eyes associated with disturbed temporomandibular joint function.

The pathology is either malocclusion from any cause or destructive changes of one or both mandibular joints. The resultant abnormal pressure in the mandibular fossa causes partial or complete closure of the internal auditory canal, accounting for the "stuffy deaf" sensation so common to the syndrome. The diverse and seemingly unconnected neuralgic pains are due to either direct nerve compression within the abnormal joint or reflex irritation of the nerves lying in close association with the joint. Therapy correcting the abnormal movement of the mandibular condyle within the mandibular fossa of the temporal bone usually relieves the patient immediately of his distressing symptoms.

The syndrome is not a rare one, Costen having collected 500 cases over a 10-year period,[2] and its recognition depends merely on considering it as a diagnostic possibility. This being the case and since the internist is often faced with the problem of bizarre facial pain, it behooves us to give Costen's syndrome more publicity in the literature on internal medicine. The three cases reported briefly below were collected over a period of three months.

REPORT OF CASES

CASE 1.—J. L. H., a 35-year-old pharmacist, complained of a "stuffy deaf" feeling in his left ear, associated with sharp pain behind the ear shooting toward the vertex. These complaints had persisted for three days despite the use of codeine sulfate, 60 mg., every three to four hours, and were aggravated by swallowing, yawning, and closing the jaws firmly. Examination revealed no abnormalities of the ear and the absence of the four lower posterior molar teeth on the left. The teeth had been removed six years previously. A gauze pledget was inserted in the space created by the missing teeth, and the patient was instructed to "bite down" hard. The pain and deafness disappeared immediately and returned as soon as the gauze was removed. He was advised to obtain dentures.

1. Costen, J. B.: A Syndrome of Ear and Sinus Symptoms Dependent upon Disturbed Function of the Tempero-Mandibular Joint, Ann. Otol. Rhin. & Laryng. **43**:1-15, 1934.

2. Costen, J. B.: Diagnosis of Mandibular Joint Neuralgia and Its Place in General Head Pain, Ann. Otol. Rhin. & Laryng. **53**:655-659, 1944.

CASE 2.—H. M., a 65-year-old white male building contractor, complained of a "stuffed-up" left ear, associated with a "neuralgic shooting pain" along the left ala nasi and a burning pain in the pharynx and along the left lateral border of the tongue. The complaints were severest at mealtimes and had persisted for three weeks, despite use of various analgesics and nose drops and local application of heat and cold. Examination revealed a perforated tympanic membrane on the right and a gray retracted tympanic membrane on the left, the result of repeated episodes of bilateral otitis media in his youth. In addition, the five lower posterior teeth were missing bilaterally, having been extracted 16 years previously. The possibility of glossopharyngeal neuralgia was considered and ruled out by failure of the therapeutic test of cocainization of the tonsillar fauces. The pain and ear symptoms were immediately relieved by "biting down" on a gauze pledget placed in the space created by the extracted teeth on the left. The patient refused to accept the diagnosis and its explanation as plausible. He sought the aid of an otorhinolaryngologist, who made a similar diagnosis and advised him to see his dentist.

CASE 3.—E. M., a 34-year-old housewife, complained of deafness and pain in the left ear associated with vertex headache of one day's duration. She noted no increase in symptoms with chewing, swallowing, yawning, or talking. Examination revealed no abnormality of the ear but absence of the four lower posterior teeth on the left, which had been extracted five years previously. "Biting down" on a gauze pledget placed in the empty space immediately relieved all symptoms. The patient refused to accept the explanation of her symptoms as a plausible one since her "teeth were extracted five years ago" and has not been seen since.

COMMENT

Internists are often confronted with the problem of bizarre facial and head pain attributed to everything from sinusitis to psychoneurosis. If mandibular joint neuralgia were considered in the differential diagnosis, a large portion of these problems could probably be resolved. The diagnosis of Costen's syndrome depends primarily on being aware of it as a diagnostic possibility. Recognition of the syndrome and proper therapy can save the physician and the patient the usual endless series of therapeutic trials with local application of heat and cold and use of analgesics, nose drops, and sedatives.

The three patients presented all had immediate relief of symptoms when the cause for the mandibular joint malfunction, malocclusion due to missing posterior teeth, was corrected by the simple expedient of filling the empty space with a gauze pledget. In Case 2 the possibility of glossopharyngeal neuralgia, which often enters in the differential diagnosis, was also considered. Once this was ruled out by cocainization of the tonsillar fauces and the symptoms were relieved by correction of the malocclusion, the diagnosis was evident.

In the three reported patients the primary pathology was unilateral or bilateral loss of posterior teeth, with resultant malocclusion. This is the commonest and most easily remediable etiological factor.[2] Ill-fitting dentures, destructive lesions about the temporomandibular joint, malocclusing natural teeth, impacted unerupted third molars, or any local pathology resulting in overclosure of the jaws can serve as the causative factor. It should be noted that no definite time relationship exists between the onset of these underlying causal factors and the onset of the symptoms of the mandibular joint syndrome. In the three cases reported, the missing teeth had been extracted 5, 6, and 16 years prior to the onset of symptoms.

On gross examination, in addition to the local pathology and the resultant overclosure, one may find crepitus within the mandibular joint, tenderness of the joints to internal palpation, uneven jerky movement of the lower jaw on opening and closing, and even trismus, either slight or marked.[3] Roentgenograms will reveal

3. Costen.[1, 2]

the cause of the overclosure of the joint and, occasionally, local changes in the temporomandibular joint itself, such as density changes in the mandibular joint structures, narrowing of the space between the condyle and the mandibular fossa, widening of joint spaces and wide excursion of the condyle in the open position, fixation of one condyle against the tubercle and normal excursion of the opposite condyle, erosion of the anterior surfaces of the condyle and posterior aspect of the articular tubercle, and change in normal contour of the fossa (deepening) and of the condyle, but with normal bone surfaces (suggesting abnormal stress).[4]

The ear symptoms associated with the syndrome are a sense of "stuffiness" in the ear, with impaired hearing, tinnitus, and dizziness, all relieved by inflation of the Eustachian tubes, and varying degrees of ear pain. These symptoms are present in almost every case, while various combinations of occipital and vertex pain, glossodynia, and burning or dry pain in the pharyngeal wall, the eyes, and along the side of the nose may or may not be found. All symptoms are usually aggravated by eating, yawning, or laughing, and any other activity which places stress on the mandibular joint.

An analysis of the anatomy of the mandibular joint offers ready explanation for the varied and seemingly unconnected neuralgic symptoms. The chorda tympani nerve and the auriculotemporal nerve lie in close association with the joint.[5] Medially the chorda tympani nerve may be irritated, and posteriorly the auricular branches of the auriculotemporal nerve may be impacted between the articulating surfaces. Occasionally the auriculotemporal nerve itself may be irritated. Reflex pain may be produced when joint destruction is great enough to allow the eroded face of the condyle to rest against the tubercle of the mandibular fossa. Either direct or reflex irritation of the auriculotemporal nerve accounts for the otalgia.[6] The glossodynia and the pharyngeal and nose pain in the absence of local lesions are explicable on the basis of reflex pain mediated along the auriculotemporal and chorda tympani nerves to the lingual and glossopharyngeal nerves.[7]

All symptoms may be relieved immediately by proper reposition of the jaws to correct condylar malposition and its concomitant malocclusion. In the three cases reported, successful temporary therapy was effected by replacing the missing posterior teeth with a gauze pledget. The diagnosis of mandibular joint neuralgia rested ultimately on such a successful test of therapy.

SUMMARY

Three cases of mandibular joint neuralgia are briefly presented, and the causation, symptomatology, objective findings, and therapy discussed.

The importance to the internist of knowledge and recognition of the syndrome is stressed.

4. (*a*) Costen.[2] (*b*) Costen, J. B.: Reflex Effects Produced by Abnormal Movements of the Lower Jaw, Arch. Otolaryng. **36**:548-554, 1942.

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Case Reports

USE OF ELECTROCONVULSIVE THERAPY IN A CASE OF ADDISON'S DISEASE

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IT IS KNOWN that nervousness and mental symptoms may dominate the clinical picture in a patient with Addison's disease.[1] As the disease progresses, the patient often demonstrates nervous irritability, insomnia, and inability to concentrate. However, these symptoms readily disappear with adequate substitution hormonal therapy. We have been unable to find a description of a patient having Addison's disease with psychosis who received electroconvulsive therapy. The signs and symptoms of adrenal crisis have been known to develop in the course of a few hours following physical or psychic trauma or any type of severe stress. The following is a case report which should be of considerable interest to the clinician who is faced with the problem of treating an alarming psychotic episode in a patient with Addison's disease.

REPORT OF A CASE

A 56-year-old white male veteran entered the Veterans Administration Hospital, Jefferson Barracks, Mo., on June 22, 1951, complaining of weakness, fatigue, weight loss, anorexia, and constipation. He stated that he had become progressively weaker during the past two years and was incapable of any physical or mental effort; his complexion had become definitely darker. There were no febrile episodes or respiratory symptoms during the course of his illness; however, he had had a "bad case of the flu just before I got sick." Physical examination on admission revealed a tanned, profoundly weak, weary man who appeared rather dehydrated; there was evidence of recent weight loss. His temperature was 99 F.; the pulse was regular, with a rate of 90 per minute; respirations were 15 per minute. The blood pressure was 84/60. Despite the general tanned appearance of the body, there was no other evidence of hyperpigmentation, nor were there areas of vitiligo; the diffuse tan covered the nonexposed as well as the exposed parts of the body. The mucous membranes appeared normal. Muscular strength was greatly decreased. The remainder of the physical examination failed to reveal any evidence of abnormalities. Mental status was normal; there was nothing to suggest deviations characteristic of a psychosis.

Laboratory Findings.—The white blood cell count on admission was 6,500, with a differential count showing 40% polymorphonuclear leucocytes, 56% lymphocytes, and 4% eosinophiles. The hemoglobin concentration was 14.4 gm.; the red blood cell count was 5,100,000. The hematocrit reading was 49%. Fasting blood glucose was 88 mg. per 100 cc.; serum chlorides were 96 mEq.; serum sodium, 130 mEq.; serum potassium, 5.8 mEq., and carbon dioxide, 17.8 mEq. per liter. The results of urinalysis were normal. A chest roentgenogram revealed fibrocalcific

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not reflect the opinion or policy of the Veterans Administration.

1. Hartman, F. A., and Brownwell, K. A.: The Adrenal Gland, Philadelphia, Lea & Febiger, 1949.

infiltration in both apices. Repeated sputum examinations revealed no acid-fast bacteria. There were no definite abnormal changes in the electroencephalogram. A flat roentgenogram of the abdomen failed to reveal evidence of calcification in the region of the adrenal glands. The total eosinophile count was found to be 430 per cubic millimeter; there was failure to obtain a depression in the number of eosinophiles during the four-hour corticotropin test of Thorn. A Kepler-Power-Robinson test was performed; using the empirical formula, "A" was found to be 4.2. (This test definitely demonstrates, in the absence of nephritis, the three abnormalities found in Addison's disease: a decreased urea clearance, an increased chloride clearance, and a decreased water diuresis.[2])

Clinical Course.—In view of the established diagnosis, substitution therapy was begun. During the first few months of therapy, frequent adjustment in the dose of desoxycorticosterone acetate (DCA) was found necessary; pellets of desoxycorticosterone were implanted after the stabilizing dose of the drug was determined. It was found that the patient also required an oral dose of 25 mg. of cortisone daily.

The patient's strength improved so much that he was able to return to part-time work. He continued to return to the hospital for frequent observation. He had no evidence of undesirable reactions to the adrenal hormone preparations until March, 1952, when he began to become tearful, depressed, and self-accusatory. These symptoms were thought to be due to cortisone.[3] Administration of the drug was discontinued. Shortly thereafter the patient began to suffer from anorexia, and his blood pressure dropped to hypotensive levels of 60/40. He also had intractable hiccough (This symptom is often the first indication of the onset of adrenal crisis.[4]). Cortisone therapy was reinstituted, and, in addition, 2 mg. of desoxycorticosterone was given daily. Because of the evidence of considerable sensitivity to the hypertensive effect of desoxycorticosterone,[5] the dose of this drug was reduced to 0.5 mg. daily. The serum electrolytes remained essentially unchanged during these changes in therapy. However, the patient continued to suffer from distressing hallucinations and remained very depressed. It was the feeling of the psychiatrist, Dr. Alfred K. Baur, that he was definitely a suicidal risk. Accordingly, the patient was presented to the medical staff conference to consider electroconvulsive therapy (ECT), as it was obvious that he would continue under great psychic stress if allowed to remain in a state of agitation. It was the consensus that electroconvulsive therapy should be instituted. Without increasing the supplementary hormonal therapy, electroconvulsive therapy was begun on April 1, 1952. The patient received four treatments, and he has since been able to carry out normal activities. His electrolytes were studied very closely while he received electroconvulsive therapy, and at no time did he show any unusual changes in serum electrolytes. Clinically, there was no evidence of impending adrenal crisis. His condition remains controlled with the therapy instituted just prior to the electroconvulsive treatment.

COMMENT

It is well known that operative procedures on patients with Addison's disease should be attended with careful supplemental therapy prior to the surgical intervention. The care and treatment of patients following operation should be the same as that outlined for patients in adrenal crisis. Patients have undergone urgently needed electroconvulsive therapy even though they may have had coronary arteriosclerotic heart disease with a history of acute myocardial infarction. An acute

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3. Rome, H. P., and Braceland, F. J.: Psychological Response to Corticotropin, Cortisone and Related Steroid Substances, J. A. M. A. **148**:27-30 (Jan. 5) 1952.

4. Kepler, E. J.: Diseases of the Adrenals: Review with Special Reference to Clinical Aspects, Arch. Int. Med. **56**:105-135 (July) 1935.

5. Soffer, L. J., and Engel, F. L.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, J. A. M. A. **115**:1860-1866 (Nov. 30) 1940.

infectious process, such as active pulmonary tuberculosis, is not necessarily a contraindication to treatment.[6] This important empirical method of treating neuropsychiatric conditions has saved countless patients from suicide. To deny its use in a severe depression would be a tragedy indeed.

Electroconvulsive therapy was carried out in our patient without an increase in supplementary therapy. Emergency measures were always available for instant use. Prior to electroconvulsive therapy the total eosinophile count per cubic millimeter was found on two occasions to be approximately 650. Immediately after treatment, the count averaged 800; four hours following the treatment, the count was approximately the same as that found preceding treatment. In like manner, the response was studied in several other patients receiving electroconvulsive therapy. None of these patients had any evidence of adrenal cortex insufficiency. A typical response was found to be 220 eosinophiles per cubic millimeter prior to treatment, 160 immediately after electroconvulsive therapy, and 200 cells four hours following treatment. There were no serum electrolyte changes noted in these patients immediately after electroconvulsive treatment. In spite of the biochemical studies recorded by Myerson and associates,[7] it is our opinion that electroconvulsive therapy does not produce acute physiological stress. We consider that the patient should have a minimum number of treatments because of the possible biochemical changes recorded by Myerson, in particular the lowering of the 17-ketosteroid output in the urine after five or six treatments. This output was recorded as remaining decreased for six to eight weeks after termination of electroconvulsive therapy and indicates possible damage to the adrenal glands. We make a plea that electroconvulsive therapy be not denied the patient with Addison's disease who becomes depressed and urgently requires the lifesaving procedure.

SUMMARY

A patient with Addison's disease received electroconvulsive therapy because of an episode of acute, severe depression with suicidal intent. He withstood the procedure very well, without evidence of adrenal crisis. No increase of substitution hormonal treatment was required during therapy. It might be surmised that electroconvulsive therapy does not cause acute physiological stress comparable with that of severe trauma, surgical procedure, infection, etc.

6. Will, O. A., Jr., and Duval, A. M.: The Use of Electro-Shock Therapy in Psychiatric Illness Complicated by Pulmonary Tuberculosis, J. Nerv. & Ment. Dis. **105**:637-646 (June) 1947.

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OBSCURE FEVER CAUSED BY CARCINOMA OF THE KIDNEY

A Possible Explanation for the Difficulties in Diagnosis

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IT IS WELL known that malignant tumors of the kidneys are particularly prone to cause fever.[1] However, in those cases of fever caused by renal carcinoma, the diagnosis is extremely difficult and often missed. We believe the difficulties arise because in many of these cases the kidney tumors may cause little or no defect in the pelves or calyces. They apparently expand laterally rather than medially, and, therefore, the only change in the pyelogram may be a displacement of the kidney or an increase in its size.

To substantiate this concept, we have analyzed the cases in the literature in which retrograde pyelograms have been done and are reporting one case of our own.

ANALYSIS OF LITERATURE

In analyzing the literature, it is necessary to limit the discussion to those cases completely studied, especially with reference to retrograde pyelograms.

Creevy [1d] presented two cases of fever with hypernephroma. The first case was that of a woman who had temperature elevation to 100 to 102 F. from her admission to the hospital until the day of operation (two months). Retrograde pyelograms revealed large hydronephrosis and hydroureter on the left with an early dilatation of the right renal pelvis. The preoperative diagnosis was infected left hydronephrosis and early right hydronephrosis probably due to the presence of anomalous renal vessels. At operation the left kidney was found enlarged to twice the normal size. The enlargement was due to parenchymal replacement by nodules of friable

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1. (*a*) Allemann, R., and Bayer, R.: Beiträge zur Klinik der malignen Nierentumoren, Ztschr. urol. Chir. **14**:119-156, 1923 (see p. 129). (*b*) Berg, A. A.: Malignant Hypernephroma of the Kidney, Surg., Gynec. & Obst. **17**:463-471, 1913. (*c*) Costano, C. A., and Risolia, A. J.: Kidney Tumors, Semana méd. **1**:989, 1923; abstracted, J. A. M. A. **81**:1730, 1923. (*d*) Creevy, C. D.: Pyrexia in Malignant Nephroma (Hypernephroma), J. A. M. A. **92**:1256-1260, 1929. (*e*) Hamman, L., and Wainwright, C. W.: The Diagnosis of Obscure Fever: Diagnosis of Unexplained High Fever, Bull. Johns Hopkins Hosp. **58**:307-331, 1936. (*f*) Hyman, A., and Leiter, H. E.: The Association of Hypernephroma with Amyloidosis of the Kidney, J. Urol. **56**:303-309, 1946. (*g*) Israel, J.: Über Fieber bei malignen Nieren- und Nebennierengeschwülsten, Deutsche med. Wchnschr. **37**:57-62, 1911. (*h*) Loughnane, F. M.: Renal Sarcoma of Infancy, Brit. J. Surg. **2**:77-91, 1914. (*i*) Marsh, H.: On The Association of Suppuration with Malignant Diseases, St. Barth. Hosp. Rep. **23**:147, 1887. (*j*) Melicow, M. M.: Classification of Renal Neoplasm: A Clinical and Pathological Study Based on 199 cases, J. Urol. **51**:333-385, 1944. (*k*) Nicholson, D.: Fever with Renal Carcinoma, Arch. Path. & Lab. Med. **3**:393-399, 1927.

tumor tissue. Microscopic examination showed islands of large clear, polyhedral cells, often with a foamy cytoplasm. Nuclei were large and hyperchromatic. A picture of the pyelogram is shown in the article. Although the reproduction is not perfect, no evidence pointing to tumor is seen, and Creevy himself did not suspect tumor. In the second case, by way of contrast, although a definite deformity was seen on the retrograde pyelogram, the patient did not have fever preoperatively except for a few days following cystoscopy.

Hamman and Wainwright [1e] reported 44 cases of obscure fever in which diagnosis was finally made. Five of these were cases of hypernephroma. They reported one case in detail (Case 14) in which the obscure fever had persisted for four months and retrograde pyelograms were requested. The urologist considered the right upper calyx to be flattened and compressed in the pyelograms. On the other hand, the roentgenologist thought the deformity was within normal limits. The opinions of several urologists were sought, and conflicting views were given. Nevertheless, the patient was operated upon, and a tumor, 5 by 6 cm., was found in the upper pole of the right kidney. A nephrectomy was performed. The pyelograms of both the right and the left kidneys are reproduced in the paper. Undoubtedly there is a difference between the upper calyx on the right and that on the left. However, it is slight, and if one looked at the pyelograms, not knowing the diagnosis, the correct interpretation might easily be missed.

Hyman and Leiter [1f] reported on a 54-year-old woman with obscure fever (Case 3). She was examined by the authors approximately two months after the onset of the fever. Intravenous and retrograde pyelograms were normal. Four months later, a retrograde pyelogram revealed several filling defects in the left renal pelvis which were thought to be nonopaque renal calculi. Several days later, another left pyelogram was taken, and this time an irregular cavity was demonstrated in the upper pole. This was thought to be inflammatory and was not considered the cause of the prolonged fever. The patient died, and at necropsy a large irregular cavity in the upper pole of the left kidney was found encroaching upon the upper calyx. Histologic diagnoses were (1) adenocarcinoma of the upper pole of the left kidney with invasion of the left renal vein and renal pelvis; (2) tumor thrombosis of left renal vein and vena cava, and (3) amyloidosis.

REPORT OF CASE

F. W. (L. H. 33697), a 54-year-old white male machinist, entered Lebanon Hospital in the medical ward service of one of us (D. G.) on Oct. 23, 1950, complaining of fever and weakness of several months' duration. He had observed fever, the temperature ranging from 99 to 102 F. daily, for which he had received antibiotics and sulfonamides at home without effect.

On his admission to the hospital physical examination showed merely pallor and a systolic apical murmur. He began to run a spiking fever, with elevation to 99 to 102 F. Laboratory studies, including many blood cultures, numerous blood counts and urinalyses, blood agglutination tests, stool cultures, and sputum cultures, all gave normal results. Because of the anemia, the finding of a soft apical systolic murmur, and a barely palpable spleen, the diagnosis of subacute bacterial endocarditis was considered, despite numerous negative blood cultures. Intensive therapy with penicillin, streptomycin, gantrisin,® terramycin, and aureomycin, singly and in combination, was given, but the temperature continued to spike. Erythrocyte sedimentation rates were always elevated throughout his course, numerous determinations ranging around 100 mm. per hour (Westergren). Several urine cultures showed enterococci, and this fact combined with the additional history of frequency of urination for the preceding eight months directed attention to the genitourinary tract. The diagnosis of hypernephroma was suspected.

Intravenous and retrograde pyelography was done twice, and the pyelograms were reported as showing no abnormalities. Numerous roentgenograms of the chest and of the gastrointestinal tract were normal. Serial electrocardiograms showed no changes. Several blood transfusions were administered because of the anemia. However, all therapy failed to affect the temperature curve, which continued to range from normal to 102 to 103 F. daily. The patient had few complaints aside from weakness.

Fig. 1.—Retrograde pyeloureterogram. Note lateral displacement of lower pole of left kidney.

A trial of cortisone (50 mg. given orally twice daily) was begun on Nov. 28, 1950. Within two days, the temperature dropped to normal for the first time since his admission to the hospital and remained normal while cortisone was administered. As soon as the use of cortisone was discontinued on Dec. 11, 1950, the pyrexial course immediately became evident. Similar results were obtained when cortisone was subsequently administered orally in a dose of 50 mg. daily. After 73 days in the hospital, he was temporarily discharged on Jan. 10, 1951, with a diagnosis of fever of unknown origin and advised to return at a later date for further study.

At home, he continued to have a temperature of 99 to 103 F. daily, and he reentered the hospital on Jan. 18, 1951. Penicillin in doses of 12,000,000 units daily had no effect on the

spiking temperature. Repeated roentgenograms of the chest and intravenous pyelograms were normal. Again a suspicion of tumor of the genitourinary tract was entertained but could not be proved.

The patient's condition now began slowly to go downhill. Oral administration of cortisone was continued, since this appeared to be the only medication that controlled his septic temperature. Albuminuria slowly developed, along with fixation of specific gravity. On Feb. 22, blood urea

Fig. 2.—Left kidney unopened. Tumor is at lower pole.

nitrogen was 69 mg. and the creatinine was 5.7 mg. per 100 cc. He slowly sank into uremia and died on March 2, 1951, after a hospital stay of 44 days.

Autopsy was performed and showed a hypernephroid carcinoma at the lower pole of the left kidney (weight, 475 gm.) and extensive amyloidosis of the kidneys and spleen. The autopsy protocol stated that "the lower pole of the left kidney is occupied by a spherical mass slightly larger than a golf ball and causing some distortion of the shape of the kidney. This mass is

distinctly circumscribed and sharply demarcated from the adjacent renal parenchyma. The tumor has no obvious connection with the renal pelvis, although it borders on the wall of the lower calyx without producing distortion of its lumen" (Figs. 2 and 3).

The microscopic description of the kidneys was as follows (Fig. 4):

"Both kidneys are severely altered. The glomeruli are large. The loops are swollen and completely fill the capsular space. The capillary walls are thickened and contain a deeply

Fig. 3.—Left kidney opened.

eosinophilic homogeneous substance which gives a positive reaction for amyloid. Amyloid is present also in the walls of the small blood vessels.

"Throughout both kidneys, there is an increase in interstitial connective tissue, with areas of mononuclear and polymorphonuclear cellular infiltration. The tubules are almost uniformly dilated and filled with hyalin casts often intermingled with cellular debris. The tubular epithelium is flattened. In places there is hyalin droplet degeneration of tubular lining cells. Such cells are swollen, and the lumen of these tubules is narrowed. Sudan stain reveals fat droplets and many tubules. Many of the veins contain fibrin thrombi, some of which show beginning organization.

"The tumor of the left kidney has a dense fibrotic capsule. There are extensive degenerative changes, necrosis, and hemorrhage. The tumor does not invade the renal pelvis or vessels. The thrombi in the renal vessels are bland. Sections stained with hematoxylin and eosin show a solid neoplasm consisting of cords and acini of polygonal cells with pale-staining or 'clear' cytoplasm

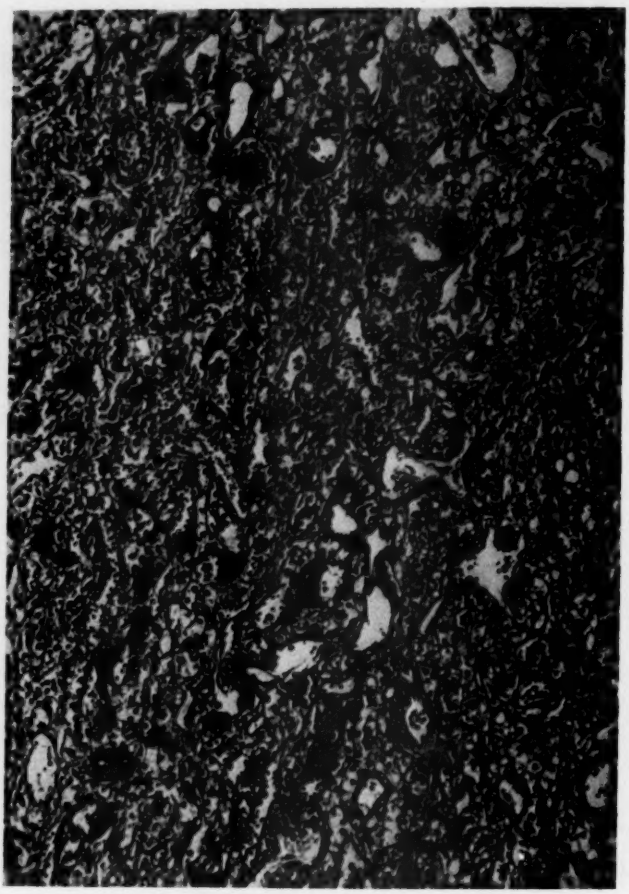

Fig. 4.—Histologic section of clear cell adenocarcinoma.

and a small, dark nucleus which is usually placed at the periphery of the cell. The cell cords are supported by a delicate stroma, which carries an extensive network of sinusoids. In many places there is a homogeneous swelling of the ground substance immediately adjacent to the lining of the sinusoids; this substance is stained intensely by eosin and gives a positive reaction for amyloid. In places the appearance of the tumor is quite uniform; however, there are areas of marked cell atypism with large hyperchromatic nuclei and deeply staining cytoplasm. Mitotic figures are rare."

COMMENT

It is obviously impossible to find all the cases of obscure fever caused by renal carcinoma. Many are hidden in other reports, and some are unreported.

Marsh [11] in 1887 reported on a child with renal sarcoma who had a pyrexial course with a temperature up to 102 F. It was Israel,[1g] however, in 1911, who first documented a series of 18 cases in which fever was the outstanding symptom. He emphasized the early appearance of fever and found malignant tumors of the kidney in 12 cases in which surgical procedures were performed. It is of interest to observe that in one of his cases in which the fever had persisted for months, "the tumor was a hypernephroma of the lower pole which had allowed the greater part of the kidney to remain intact and had no communications with the kidney pelvis." The resemblance to our case is remarkable.

Allemann and Bayer [1a] recorded five cases of hypernephroma associated with fever. Costano and Risolia [1c] observed six cases of hypernephroma, in three of which there was a febrile course that subsided after nephrectomy.

Examination of the literature and our experience show that these malignant renal tumors associated with obscure fever tend to produce minimal or no changes in the calyceal or pelvic systems, as seen on pyelography. The tumors grow laterally and may become quite large without showing marked defects in the pyelograms. One should not rely, therefore, upon the usual criteria of tumor diagnosis when studying the pyelogram in a case of obscure fever. Rather, the shape, size, and position of the kidney are the significant factors to be noted. Such changes are not unusual. Melicow,[1j] in discussing 36 cases of renal carcinoma reported: "The pyelograms were not characteristic of tumor in eight, of which six showed only an enlarged kidney." Unfortunately, he did not correlate the pyelograms with the occurrence of fever.

In the case presented in this paper, the only significant findings on the pyelograms were lateral rotation of the lower pole of the left kidney and an increase in parenchymal shadow in this area. These were hindsight interpretations discovered on attempting to correlate the pathological findings with the clinical studies (Fig. 1).

The development of amyloidosis in this patient while under observation was also of considerable interest. Hyman and Leiter [1f] reported a similar finding in association with carcinoma of the kidney.

SUMMARY

A case of obscure fever is reported in which the ultimate diagnosis was carcinoma of the kidney with minimal or no changes visualized in the pyelogram. Uremia secondary to extensive amyloidosis was the cause of death. The literature concerning similar cases is reviewed. We should like to emphasize that in those cases of obscure fever due to renal carcinoma pyelograms may be misleading and show relatively few changes.

ADDENDUM

Shortly after this article was written, a paper on this subject by Hempstead and Priestley [2] appeared.

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2. Hempstead, R., and Priestley, J. T.: Fever as a Predominant Symptom of Hypernephroma: Report of 2 Cases, Proc. Staff Meet., Mayo Clin. **27**:67-70, 1952.

GANGRENE OF AN EXTREMITY SECONDARY TO VENOUS THROMBOSIS

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EXTENSIVE venous occlusion of an extremity leading to gangrene is a relatively rare occurrence, as judged from a review of the literature.[1] The opinion, however, has been expressed that undoubtedly many cases of gangrene occur in which the true nature of the underlying disease is not recognized and which, therefore, are attributed to arterial occlusion.[2] It is for this reason that we wish to call attention to the serious complication of venous thrombosis by reporting a case which was recently observed by us.

Haimovici,[1] in an extensive review of the literature up to 1949, collected 28 cases of gangrene of an extremity on the basis of massive venous occlusion. In two of these patients the involvement was bilateral. The incidence of gangrene in the lower extremities was about 80%, in the upper, 20%. The ages varied from 8 to 69 years, with almost equal distribution in the sexes. The etiological circumstances leading to venous thrombosis were postoperative status in six patients, postpartum status in four, post-traumatic status in six, and visceral malignant neoplasm in two; miscellaneous causes were recorded in six. The cause was unknown in four.

Veal and associates [2] reported on two additional patients with unilateral gangrene, in one post partum, in the other following massive venous thrombosis after sclerosing therapy. One other case was recently reported by Grant and Deddish [3] in which the venous occlusion was associated with carcinoma of the rectum with metastases to the liver.

The characteristic symptoms which should lead one to suspect this condition are extensive edema, usually involving the entire extremity, associated with blanching of the skin in the early phases followed rapidly by blue discoloration, coldness, and severe pain that may be sudden in onset or progressive. Arterial pulses are palpable in about one-third of the patients, while in the remaining two-thirds the distal arterial pulsations cannot be felt. The disappearance of pulses may be caused by

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2. Veal, J. R.; Dugan, T. J.; Jamison, W. L., and Bauersfeld, R. S.: Acute Massive Venous Occlusion of the Lower Extremities, Surgery **29**:355-364, 1951.

3. Grant, R. N., and Deddish, M. R.: Phlegmasia Cerulea Dolens and Gangrene, New York J. Med. **52**:584-585, 1952.

the extensive edema or may be the result of the secondary arterial spasm which is frequently associated with thrombophlebitis. However, the experience of most observers that vasodilator drugs, as well as autonomic nerve blocks, are of little therapeutic value would lead one to conclude that vasoconstriction plays a relatively insignificant role in the abolition of the arterial pulsations.

The outstanding pathologic features of this entity consist of massive obstruction by thrombus of practically all venous channels associated with gangrene, usually of the distal portion of the involved extremity, and complete patency of the arterial tree. On microscopic section of the arterial system the lumen is always empty and patent. The prognosis is poor. Thirteen of the 31 patients previously reported on died, as did the subject of this report. Only three patients, each of whom had minor gangrene, recovered without surgical intervention. The remaining patients required major amputations as lifesaving measures.

The treatment is quite unsatisfactory. As pointed out above, sympathetic nerve blocks and vasodilator drugs have not been found to be of great value. DeBakey [4] was able, in one patient, to open sufficient pathways by surgical removal of a venous thrombus to cause regression of an early gangrene and thereby prevent amputation. Anticoagulant therapy has no effect on the already established venous obstruction and, thus, is not useful in the treatment of the gangrene until blood flow has been reestablished by one means or another, if such reestablishment is at all possible. However, anticoagulants may be of value in preventing propagation of the thrombus proximally and in reducing the likelihood of pulmonary emoblization. Amputation remains the only recourse in cases of extensive gangrene.

REPORT OF A CASE [5]

History.—C. K. W., a 54-year-old white man, had symptoms of belching and epigastric distress for a number of years. A gastrointestinal series in May, 1950, was reported as showing duodenal irritation. In August, 1951, the patient noted severe lower back pain and nausea. A repeat gastrointestinal series at that time was reported to be normal. Two months later, the patient noted anorexia, vomiting, epigastric pain, and marked weight loss. An intravenous pyelogram, sigmoidoscopic examination, and barium enema visualization at another hospital revealed no abnormality. The symptoms progressed, and on Nov. 27, 1951, the patient was admitted to this hospital.

On physical examination he was well developed, but poorly nourished, and appeared chronically ill. The sclerae were slightly icteric, and the tongue was smooth. The lungs were clear to percussion and auscultation. The heart was normal except for occasional premature contractions. The liver was enlarged 1 fingerbreadth below the right costal margin and extended into the epigastrium, and a tender nodular mass was palpable deep in the lower epigastric region. The left testis was enlarged, and scrotal varices were present. Enlarged axillary nodes were noted on the right.

There was moderate anemia with mild leucocytosis. Serum bilirubin was 1.5 mg. per 100 cc.; the cephalin flocculation was 2 +; the serum alkaline phosphatase was 20.2 Shinawara units, and a sulfobromophthalein (bromosulphalein®) sodium test showed 22% retention in 45 minutes. Roentgenographic examinations of the chest, lumbosacral spine, and large bowel showed no abnormality. A gastrointestinal series, however, showed forward displacement of the lower end of the stomach on lateral views.

The patient's condition became progressively worse. On Dec. 10, 1951, a liver biopsy was performed, and anaplastic adenocarcinoma was found. The clinical diagnosis, in view of the

4. DeBakey, M., and Ochsner, A.: Phlegmasia Cerulea Dolens and Gangrene Associated with Thrombophlebitis: Case Report and Review of Literature, Surgery **26**:16-29, 1949.

5. Clinical abstract is by Dr. A. A. Polachek, of the Medical Service.

findings on the gastrointestinal series, was adenocarcinoma of the body of the pancreas with metastases to the liver.

On Dec. 29, painless pitting edema of the left leg was noted. There was no elevation of local temperature and no calf tenderness; Homans' sign was not elicited. Two days later the patient noted pain in the left great toe, which was bluish-black, cold, and anesthetic. The second, third, and fourth toes were slightly cyanotic. The foot and popliteal artery pulses were absent on that side, but the femoral pulse was strong. All pulses on the right side were present. On the following day, Jan. 1, 1952, the left femoral pulse had become weaker, cyanosis of the foot was more intense, and at this point the nature of the gangrenous process was suspected (clinical progress note by Dr. A. D. Renzetti, of the Medical Service). The patient was seen in consultation by staff members of the peripheral vascular disease clinic (Dr. Karl Harpuder, Senior Consultant), and a diagnosis of gangrene of venous origin was made (Fig. 1). After a left paravertebral block, a faint pulsation was felt in the dorsalis pedis artery. Treatment with heparin and priscoline® (2-benyl-2-imidazoline) hydrochloride intra-arterially was, therefore, begun, but the patient's general status deteriorated rapidly, and he died on Jan. 4, 1952.

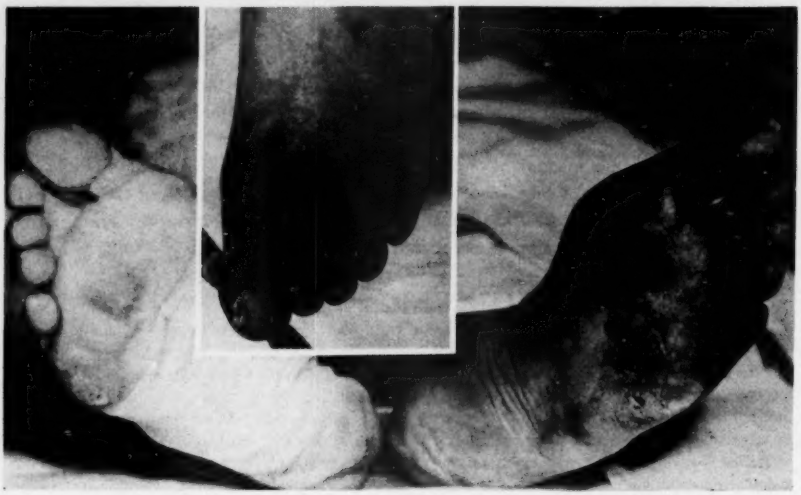

Fig. 1.—Gangrene of left foot, dorsal and plantar views.

Autopsy Observations.—There was 4 + pitting edema of the left lower extremity extending up to the inguinal ligament. The toes and a small portion of the adjoining dorsum of the foot were dark purple, but the skin was intact. A large tumor was found arising in the body of the pancreas. Microscopic examination showed this to be an adenocarcinoma. The regional lymph nodes were replaced by metastatic tumor. There were massive metastases in both lobes of the liver, as well as in the hilus. There was marked bile retention due to intrahepatic and extrahepatic obstruction of the bile ducts by tumor.

Multiple venous thromboses of the viscera and of the left lower extremity were present. The thromboses noted in the viscera were related to the spread of the tumor. Thus, the splenic and inferior mesenteric veins and the portal vein at the liver hilus were embedded in tumor and completely occluded by thrombus. However, the thromboses of the left lower extremity were not associated with the tumor. The entire venous system of the left leg, from the common iliac to the metatarsal veins, was occluded by thrombus (Figs. 2 and 3).

The lower portion of the propagating thrombus was firmly adherent to the vein walls. It consisted largely of masses of homogeneous, palely eosinophilic material, with an admixture of red and white blood cells. In some areas, the periphery of the thrombus showed early organi-

Fig. 2.—Arteries and veins of the left lower extremity. Arteries are consistently patent, whereas veins are filled with thrombus. Retraction of thrombus is an artifact due to processing of the sections. *A*, left femoral artery and vein. *B*, left popliteal artery and vein. *C*, left posterior tibial artery and veins. *D*, left dorsalis pedis artery and veins. Hematoxylin and eosin stain; × 12.

zation with the creation of small collateral venous channels. It was often difficult to identify the margin between the thrombus and the intima of the vein. However, the vein walls showed no inflammatory changes, except for infiltration of rare polymorphonuclear cells which were a reaction to the thrombus (Fig. 3*B*). There were no thrombi in the corresponding arteries, which were patent although the seat of moderate medial arteriosclerosis. There was no inflammation in the wall of the arteries or in the adventitia. The prostatic and pampiniform plexuses of veins were also occluded by thrombi. No metastatic tumor or enlarged regional lymph nodes were found in the region of the prostate or in the lower extremity.

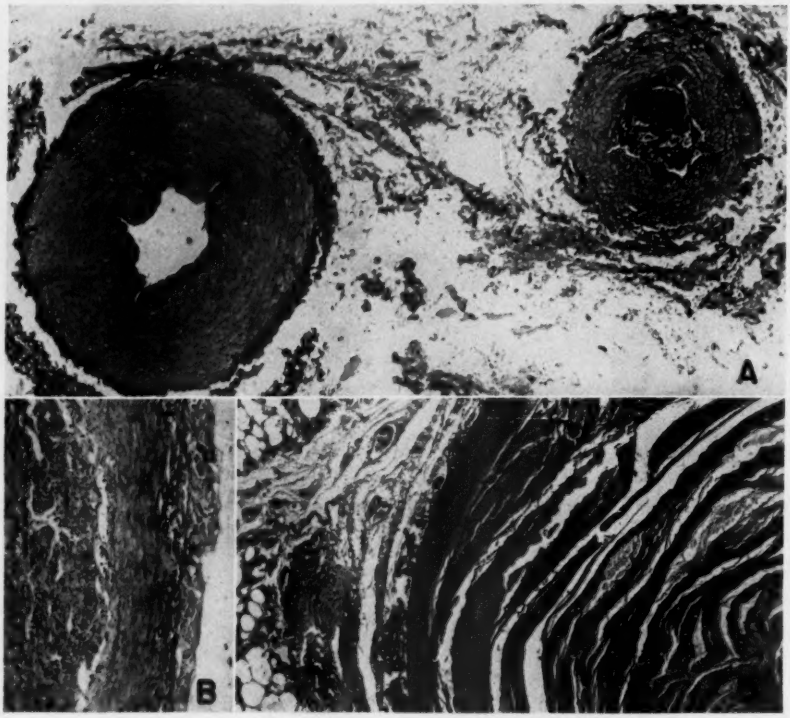

Fig. 3.—*A*, higher power view of dorsalis pedis artery and vein. Thrombus fills lumen of vein and merges with endothelium. Hematoxylin and eosin stain; × 33.3. *B*, segment of wall of left posterior tibial vein showing adherent thrombus. Note absence of inflammatory reaction in wall of vein. Hematoxylin and eosin stain; × 83.3. *C*, segment of pulmonary artery with thrombus which was immediate cause of death. Hematoxylin and eosin stain; × 13.4.

The immediate cause of death was a massive pulmonary embolus (Fig. 3*C*). This undoubtedly occurred shortly before death, since no infarcts were found in the lungs, but only moderate congestion and edema and a few patches of bronchopneumonia. Multiple small healing infarcts were scattered through the kidneys and spleen. These emboli probably originated in the heart, where friable masses of degenerative verrucous endocardiosis[6] were found in the aortic and mitral valves.

6. Allen, A. C., and Sirota, J. H.: Morphogenesis and Significance of Degenerative Verrucal Endocardiosis (Terminal Endocarditis, Endocarditis Simplex, Non-Bacterial Thrombotic Endocarditis), Am. J. Path. **20**:1025-1056, 1944.

Final Diagnoses.—The final diagnoses were as follows: (1) adenocarcinoma of body of pancreas with metastases to liver and pancreatic lymph nodes; (2) thrombosis of all veins of left lower extremity, left common iliac vein, prostatic plexus, both pampiniform plexuses, and portal, splenic, and inferior mesenteric veins; (3) gangrene of left foot; (4) pulmonary emboli, bilateral, massive; (5) congestion and edema of lungs; (6) degenerative verrucous endocardiosis of mitral and aortic valves; (7) organizing infarcts of spleen and kidneys; (8) bronchopneumonia, bilateral, and (9) generalized arteriosclerosis, moderate.

COMMENT

In this case there was gangrene of a lower extremity due to massive venous occlusion in that limb in a patient whose primary disease was adenocarcinoma of the body of the pancreas. The association of multiple venous thrombosis with carcinoma of the body and tail of the pancreas, clinically well known, was reviewed first by Sproul [7] and more recently by Kenney.[8] The latter, in a group of 9,800 autopsies, found 30 cases of carcinoma of the head of the pancreas, of which 5 were associated with a single thrombosed vein and none with multiple thromboses. In the same group there were 21 cases of carcinoma of the body or tail of the pancreas, and, of these, 7 showed multiple venous thrombi and 10 had at least one thrombus. It is interesting to note that, in spite of the frequent occurrence of multiple thromboses in carcinoma of the pancreas, there have been no previous reports of gangrene resulting from such venous occlusion.

In this case the venous occlusion was in the nature of a phlebothrombosis rather than a thrombophlebitis. Ochsner and DeBakey [9] pointed out the significant difference between these two types of venous clotting. In thrombophlebitis the clot is associated with and dependent upon inflammation of the vein wall. The inflammation may extend to the perivenous tissue. On the other hand, in phlebothrombosis the intravascular venous clot is not associated with any significant degree of inflammation. It may be difficult at times to distinguish between these two forms, inasmuch as in phlebothrombosis the clot may elicit a varying degree of inflammatory reaction in the wall of the vessel. However, this reaction is of a limited nature and does not extend into the perivenous tissue. Such inflammation is incidental to the stasis and is not the precipitating factor.

Most authors who have reported instances of massive venous occlusion with gangrene refer to the underlying cause as thrombophlebitis. Haimovici [1] described a phlebitis of variable intensity, as well as a periphlebitis which may extend to the adventitia of neighboring arteries. To this periphlebitic inflammation he attributed an important role in the production of arterial spasm. Other reports are less specific in their pathologic description and do not differentiate critically between thrombophlebitis and phlebothrombosis. A review of the previously published cases does not always permit this distinction because of the paucity of histopathologic data reported. Some of the reports, however, are adequately documented. Among these are two cases in which there was a thrombophlebitis with inflammation of all coats of

7. Sproul, E. E.: Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis, Am. J. Cancer **34**:566-585, 1938.

8. Kenney, W. E.: The Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi, Surgery **14**:600-609, 1943.

9. Ochsner, A., and DeBakey, M.: C. Jeff Miller Lecture: Thrombophlebitis and Phlebothrombosis, South. Surgeon **8**:269-286, 1939.

the veins.[10] On the other hand, two cases are reported in which there was no appreciable inflammation of the veins or of the perivenous tissue and which were undoubtedly cases of phlebothrombosis.[11] Veal and coworkers[2] referred to 11 patients with massive venous occlusion, 2 of which progressed to gangrene. Only 3 of these 11 patients presented clinical evidence of thrombophlebitis. It is, therefore, evident that gangrene due to massive venous thrombosis can occur as a result of thrombophlebitis or phlebothrombosis. Inasmuch as gangrene does occur after phlebothrombosis, it is not always possible to attribute the arterial spasm to the extension of perivenous inflammation to the arterial adventitia.

Veal and colleagues[2] have reported experimental evidence in support of the mechanical factors involved in the development of this form of gangrene. Obstruction by ligation of the venous return flow of a loop of small bowel and attached mesentery in a dog resulted in no change in arterial pressure until the venous pressure had reached a level 14 times greater than the initial venous pressure. They stated that arterial pulsations were hardly demonstrable and that the blood flow came to a standstill when venous pressure reached its peak. The arterial channels remained patent, and spasm was not noted. The bowel presented a deep purple appearance, and edema and petechial hemorrhages were seen in the mesentery. This is an experimental counterpart of the case presented in this report, i. e., mechanical occlusion of the entire venous system without inflammation, without arterial involvement, and without significant arterial spasm, leading to edema, cyanosis, and gangrene.

The pathogenesis of this form of gangrene was investigated experimentally by other means. Wertheimer and others[12] produced muscle necrosis by occluding the entire venous outflow with a carbon-gelatin suspension, leaving the arterial tree intact. Leriche and Jung[13] in experiments on dogs demonstrated the extremely rich venous collateral circulation which normally exists. By ligation and simultaneous sclerosing injection of the large veins of the lower extremities they produced only transitory edema. Fontaine and co-authors[11b] corroborated this finding and carried the experiment one step further by attempting to produce gangrene by total venous blockage. Not until the entire venous return flow of the base of the limb was severed, leaving the artery and nerve intact, did gangrene occur.

There is considerable evidence, therefore, in favor of mechanical obstruction of the venous system as a basic cause of this type of gangrene. Incidental to the massive venous thrombosis there may be some degree of reflex arterial spasm.

10. Decoulx, P., and Bastien, P.: Gangrène par spasme artériel au cours d'une phlébite, Ann. anat. path. **16**:353-359, 1939. Bergeret, A.; Guillaume, A. C., and Delarue, J.: Gangrène ischémique du membre inférieur par thrombose oblitérante de la totalité des veines, ibid. **9**:536-541, 1932.

11. (*a*) Wertheimer, P., and Frieh, P.: Thromboses veineuses, oblitérations artérielles et gangrène des membres: Documents cliniques, Presse méd. **43**:1004-1008, 1935. (*b*) Fontaine, R.; Israël, L., and Souze Pereira, A.: Apropos d'un cas de thrombose de la veine cave inférieure: Thrombophlébites simulant les embolies artérielles et gangrènes d'origine veineuse, J. chir. **47**:928-949, 1936.

12. Wertheimer, P.; Dechaume, J., and Frieh, P.: Infarctus musculaire d'origine veineuse: Documents expérimentaux, Lyon chir. **34**:224-228, 1937.

13. Leriche, R., and Jung, A.: Recherches expérimentales sur les oedèmes chirurgicaux des membres d'origine phlébitique, J. chir. **37**:481-495, 1931.

Evidence for this exists in the case presented here, since sympathetic block resulted in return of faint arterial pulsations. Consequently, use of vasodilator drugs and measures aimed at release of vascular spasm, such as paravertebral block or sympathectomy, would be of limited value. In effect, as pointed out by Veal and co-workers,[2] the rationale of this treatment must be seriously questioned. Interruption of sympathetic pathways with release of arterial spasm results in increased flow into a vascular bed from which there is no exit. The result is an increase of edema without an increase in effective circulation.

Veal and associates[2] have suggested exercise and extreme elevation of the extremity as a means of overcoming vascular congestion. This form of treatment probably carries with it certain risks, notably the dislodging of large thrombi, and, therefore, requires further evaluation.

SUMMARY

Massive venous occlusion of the left lower extremity resulted in gangrene of the foot in a case of adenocarcinoma of the pancreas.

The occlusion was due to phlebothrombosis of the entire venous system from the iliac to the dorsalis pedis veins. The corresponding arteries were patent. The immediate cause of death was massive pulmonary embolism which occurred notwithstanding anticoagulant therapy.

The pathogenesis and therapeutic implications are discussed. This case lends support to the view that this type of gangrene is the result of mechanical obstruction of the venous return flow and that arterial spasm is incidental.

Dr. A. S. Jacobson and Dr. A. A. Polachek, of the Medical Service, made the clinical data available.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1951

STANLEY COBB, M.D.
BOSTON

AS THIS review goes to press, there comes from England the news of the death of Sir Charles Sherrington in his 95th year. A brilliant man has passed into medical history, great because of his industry and insight, beloved because of his modesty and humanity. For the past 15 years he has been in retirement, suffering from arthritis, but intellectually active to the last, interesting himself in general problems of physiology, psychology, and history. His last contribution to the field of neurology and psychiatry was the talk he gave for the British Broadcasting Corporation in 1950 introducing a series of broadcasts on "The Physical Basis of Mind." [1] Although his experimental work had largely to do with spinal reflexes and the motor system of the brain, he was always thinking of broad principles. The word *integration* will always be associated with his name, for his great book "The Integrative Action of the Nervous System" published in 1906, is a landmark in medical evolution. Moreover, it is largely because of Sherrington's teaching that neurology is today a subject taught dynamically by neurologists who think in terms of the way in which the central nervous system works, in terms of integration and disintegration of function.

His work on the physiology of the nervous system is truly monumental. Between 1895, when he became Professor at the University of Liverpool, and 1935, when he retired as Professor at Oxford University, his bibliography contains 255 items. These contributions are scattered through many journals, but fortunately for the student the work has been remarkably well summarized in three books: first in his own "Integrative Action" [2]; secondly by John Fulton in "Muscular Contraction and the Reflex Control of Movement," [3] and finally by Denny-Brown in his definitive "Selected Writings of Sir Charles Sherrington." [4] Some of the contributions of especial importance for neurology are those on the descriptions of the spinal and the decerebrate animal, the proofs of reciprocal innervation, deep sensibility, the postural reflexes, and central inhibition; in addition, there is the work on the motor area of

1. Physical Basis of Mind: A Symposium, edited by P. Laslett, Oxford, Basil Blackwell & Mott, Ltd., 1950.

2. Sherrington, C. S.: The Integrative Action of the Nervous System, Silliman Memorial Lecture, Yale University, New York, Charles Scribner's Sons, 1906.

3. Fulton, J. F.: Muscular Contraction and the Reflex Control of Movement, Baltimore, Williams & Wilkins Company, 1926.

4. Denny-Brown, D.: Selected Writings of Sir Charles Sherrington, New York, Paul B. Hoeber, Inc., 1940.

the primate cortex. The meaning of this rich material for psychology is less explicit, but nonetheless great. In this necessarily brief notice, let us be satisfied with two quotations:

> In the multicellular animal, especially for those higher reactions which constitute behaviour as a social unit in the natural economy, it is nervous reaction which *par excellence* integrates it, welds it together from its components, and constitutes it, from a mere collection of organs, an animal individual.

This is from his Silliman Lectures in 1906.[5]

In 1933 in the Rede Lecture [5] he said:

> I may seem to stress the preoccupation of the brain with muscle. Can we stress the preoccupation too much when any path we trace in the brain leads directly or indirectly to muscle? The brain seems a thoroughfare for nerve-action passing on its way to the motor animal. It has been remarked that life's aim is an act, not a thought. Today the dictum must be modified to admit that, often, to refrain from an act is no less an act than to commit one, because inhibition is coequally with excitation a nervous activity.

THE NERVE IMPULSE

"The Electrical Activity of the Nervous System" by Brazier [6] is a small book that summarizes well and explains in simple language the essentials of a difficult field. A brief chapter on physiology introduces the subject. The action potentials, the excitability, and the propagated impulse of the peripheral nerve are discussed, leading up to a description of the electrical activity of the brain and the electroencephalogram in man. Here are given important biological and physical data, illuminating to many physicians who take the electroencephalograph as a clinical tool but know little of its physiological basis.

The argument between the supporters of the electrical theory of the nerve impulse and the advocates of the humoral theory has been largely decided in favor of the former. Of course, the nerve impulse is not an electrical current. It is discontinuous and far too slow to be anything of that sort. But if one accepts the electrical theory of nerve transmission, the discontinuity is explained by the fact that transmission of the impulse is the result of local electrical circuits between axon and surrounding membranes. Each local circuit acts as the exciting agent for the next adjacent segment of resting nerve. In other words, the nerve impulse is a reversible electrochemical reaction in which the nerve fibers within their membranes behave like core conductors. The chemical change is due to the change in the concentration of potassium and of sodium ions inside and outside the axon, the sheath of the axon acting as a semipermeable membrane.

At the synapse the eddy currents of the presynaptic fiber stimulate the postsynaptic fiber in the dendrite of the next cell across the cell membrane. Where nerve terminates in muscle or gland, there is another mechanism. At the neuromuscular junction cholinesterase is found in greater concentration than elsewhere in the muscle, and the junction is exceedingly sensitive to acetylcholine. Probably the current flow that stimulates the muscle fiber is dependent for its development upon the for-

5. Sherrington, C. S.: The Brain and Its Mechanism, London, Cambridge University Press, 1933.

6. Brazier, M. A. B.: The Electrical Activity of the Nervous System, New York, The Macmillan Company, 1951.

mation of acetylcholine, which is inhibited by the enzyme cholinesterase. Thus, the transmission at the neuromuscular junction is a special phenomenon and cannot be used as a prototype for transmission of the nerve impulse in the axons of the central nervous system and peripheral nerves.

An imposing volume that brings many subjects up to date is "Modern Trends in Neurology,"[7] edited by Anthony Feiling and largely written by British neurologists. The first chapter is the shortest and most fundamental. It is a statement of present views on conduction of the nerve impulse by Rushton, of Cambridge University. He believes that the theory of Bernstein and Lillie has been upheld by the work of the last few years. This theory considers the nerve impulse to be electrical, in that when a nerve was active at any point it produced a local electrical current which excited the neighboring points and made them in turn active. The traces of acetylcholine found along active nerves are probably not significant, whereas the large amounts found at neuromuscular junctions are important. In short, along the nerve fiber transmission is electrical; from the endings of peripheral nerves it is pharmacological. In general this agrees with Brazier's point of view.

Chapter III is an excellent review of headache by Kunkle and Wolff; it abstracts extensive work of Wolff and his collaborators in 33 pages, giving the physiological explanation of pain in the various cranial structures and a useful summary of the various kinds of headaches and their treatment. Other chapters give similar summaries, bringing information up to date on meningitis, poliomyelitis, radiculitis, cerebral tumor, abscess, aneurysms, myasthenia gravis, epilepsy and diagnostic electroencephalography, and neuroradiology.

The section on syphilis of the nervous system is an especially authoritative paper by Worster-Draught. It shows the great changes that have occurred in the treatment of neurosyphilis in the last 10 years. Penicillin is now the great antisyphilitic agent, often combined with a follow-up treatment by malaria or other pyrexial agent. The intrathecal administration of penicillin is deplored, as it leads to arachnoiditis and severe clinical reactions. Given by the cisternal route, it is especially dangerous. Arachnoiditis is discussed as a clinical entity by Elkington in Chapter V. He believes the pathology to be a low-grade, nonspecific reaction in an avascular membrane to numerous kinds of inflammatory irritants, both bacterial and chemical. The reaction leads to the development of fibrous bands and cysts which comprise the nervous structures especially in the spinal cord and base of the brain. The causation is most commonly a pyogenic meningitis, but use of spinal anesthetics, iodized oil (lipiodol®) or penicillin is to be remembered as a possible cause of progressive and incapacitating lesions causing paraplegia and focal epilepsy.

THE FRONTAL LOBES

A monographic discussion of "The Frontal Lobes and their Functions," by Denny-Brown, is found in the 76 pages of Chapter II.[7] This is a scholarly work, difficult to read but well worth careful study, for it presents original ideas in a field where they are much needed. Too much of the mass of literature on localization of function in the sensorimotor and frontal areas is physiologically naive. Denny-

7. Modern Trends in Neurology, edited by A. Feiling, New York, Paul B. Hoeber, Inc., 1951.

Brown's point of view is essentially physiological and Sherringtonian. He presents data from many fields, and his conclusions are careful. Some of them are provocative. It is refreshing to find an author who includes the Rolandic area in the frontal lobes and clearly states that the anatomical division of frontal from parietal lobe at the Rolandic fissure is arbitrary and not physiological. In fact the Rolandic fissure was probably developed because of the great need for more cortical surface for the sensorimotor mechanisms.

Frontal cortex can be classified cytologically into three groups: (*a*) the agranular precentral; (*b*) the granular frontal, and (*c*) the limbic areas on the mesial surface. Between these are transitional areas not easily classified by microscopic examination. Another division of the frontal areas is made according to the sort of response given to electrical stimulation. Denny-Brown believes that "electrical excitability as such, has no longer any specific meaning, for all cerebral cortex, in one sense or another, is excitable by electrical stimulation." The results in the agranular precentral cortex are well known; they have relatively stable motor patterns, but even here one should not speak of "centers" or focal "representation." Functions are represented in numerous areas. "It is doubtful whether, for example, a hand area or a foot area means more than a local preponderance of connexion." The limbic and orbital areas of cortex give stereotyped responses in which vasomotor effects and arrest of respiration are prominent; some areas respond to stimulation with suppression of postures, and others give licking, chewing, and salivation. On the frontal pole (granular frontal, areas 9, 10, and 11) there is no convincing evidence of excitability except the general "expectancy" reaction. This the author believes to be an indication of potentiality for extensive facilitatory effects. He emphasizes the multiple representation of functions in the cortex and explains this multiplicity on the ground of the adequate physiological stimulus to which each mechanism is designed to respond. Obviously the exploring electrode of the physiologist is nothing like the normal, adequate physiological stimulus. The idea that the two were similar has led to too many and too simple ideas of cortical function.

A polemical paper by Walshe[8] criticizes roundly all those neurologists who make maps represent cortical function. He says quite rightly that the modern operational view of experimental procedures would consider that such maps are simply a way of showing on a diagram what a certain type of experiment yields. The fact that the electrical stimuli used to elicit the responses resemble very slightly the normal adequate stimulus to these areas must be taken into account. He supports Denny-Brown's point of view and says:

> In truth, the validity of the fixed mosiac conception of the cortex in so far as the representation of movements is concerned—and it is with this alone that we are here concerned—received what should have been its death blow in the classical paper of Leyton and Sherrington (1917) and in the contemporary papers (1912-1916) of Graham Brown in the *Quarterly Journal of Experimental Physiology*. The importance of these researches lay in their discovery and description of the phenomena of primary and secondary facilitation, of deviation and reversal of response.

8. Walshe, F. M. R.: On the Interpretation of Experimental Studies of Cortical Motor Function: With Special Reference to the "Operational View" of Experimental Procedures, Brain **74**:249, 1951.

Under the conditions of their experiments it appeared that a given cortical point might first yield one movement and later another and different one, and conversely, that a given movement might be yielded now by one point and later by another and a different point that formerly did not yield it on stimulation. The appearance—and I use the word "appearance" deliberately—was that of a kaleidoscope of representation, and in the constantly dissolving scene the fixed mosaic lost forever its validity as a representation of cortical processes.

The function of the precentral cortex was discussed in this review in 1946.[9] At that time I said:

It seems to me that the much argued question as to whether the "motor cortex innervated muscles or movements" has not yet been answered. The evidence strongly suggests, however, that the normal function of the motor cortex always has to do with movements, although artificial means of stimulation of area 4 can elicit contractions of single muscles or even parts of muscles.

A recent paper by Liddell and Phillips[10] brings new evidence that would seem to answer the question and to show that the classical motor maps do not represent normal physiology. Their work indicates that Walshe has reason for his tirade against "the conception of the motor cortex as a mosaic of continuous points in each of which a muscle is uniquely and fixedly represented." Walshe's paper is worth reading; besides containing much interesting history and physiology, it is a delightful example of polite invective. Perhaps at times he imputes beliefs to his adversaries which they do not hold. I enjoyed all the paper except the neologism "areation" (page 265).

Denny-Brown[10a] believes that the effects of ablations of areas of cortex in man and in monkeys cannot be conceived of as the removal of functional "centers." One must think more of general coordinating mechanisms with differences in natural stimulus. This puts the explanation of focal reaction where it belongs, in the understanding of the activating mechanism, the "adequate stimulus." He considers visual stimuli of especial importance to frontal areas. Tactical, proprioceptive, and auditory stimuli are also important. He believes that the normal cortex has some sort of equilibrium, so that the abolition of one sort of reactions results in hypersensitivity to others. Thus, the explanation of frontal lobe syndromes is to be sought in terms of loss of adequate stimulus. This brings up the question of "release" of function in the Jacksonian sense. Denny-Brown believes that two types of released function can be recognized as resulting from frontal lesions. The first is *spasticity*, which he considers a release of proprioceptive reactions from the contactual responses that normally trigger them. This is a release of a subcortical reaction from cortical conditioning. The second is *hyperactivity*, which results from disequilibrium between the different parts of the cortical effector mechanism. Arguing in this physiological way, the author summarizes the clinical evidence and concludes that the defects in behavior due to frontal lesions in man have to do with a loss of proper response to visual events projected in time.

The difficulty is abstract, projected in time and space and directly concerned with visualizing motor and affective resultants. It is more dynamic than "imagination." It is this inability to visualize consequences which is the unique effect of leucotomy.

9. Cobb, S.: Review of Neuropsychiatry for 1945, Arch. Int. Med. **77**:576, 1946.

10. Liddell, E. G. T., and Phillips, C. G.: Overlapping Areas in the Motor Cortex of the Baboon, J. Physiol. **112**:392, 1951.

10a. Denney-Brown, D., in Modern Trends in Neurology,[7] Chap. II.

The point of view concerning lobotomy expressed by Fulton, discussed in the next section under neurosurgery, is quite different.

ADVANCES IN NEUROSURGERY

Neurosurgery is perhaps the most difficult branch of medicine. Neurosurgeons must go through a long and varied discipline before they can take the responsibility of operating on the human brain. One admires their courage and patience but realizes the necessity for the rigorous training, because their responsibility in changing the functions of the central nervous system is even greater than the responsibility for life and death. To save a man's reason may be a greater service than saving his life, but to change a man's personality may be worse than killing him.

Neurosurgery began as surgery of traumatic cerebral injuries; it progressed to the removal of tumors about 1900, and began its fateful course of changing the function of the nervous system to relieve symptoms when chordotomy was introduced in 1912. "Psychosurgery" began with "frontal leucotomy" in 1936. At the meeting of the Association for Research in Nervous and Mental Disease on "Treatment in Psychiatry" on Dec. 15, 1951, in New York, an afternoon was devoted to discussion of neurosurgical treatment. Operations on the cerebral frontal areas, on the anterior and medial parts of the temporal lobe, and on the cingulum and thalamus were described. Fulton, in concluding his Salmon Lectures of 1950,[11] said:

> The implications of lobotomy are vast, for the neurosurgeon is in fact dissecting the matrix of the mind with the end in view of correcting faulty structure and interrupting the vicious circles which form the basis of abnormal mental states.

This epigrammatic sentence strikes at the core of the problem, but could perhaps be modified by saying that what the surgeon usually accomplishes, if he is successful, is improvement of faulty function by interfering with normal structures in such a way as to cause a more comfortable, though somewhat lower, level of total integration.

Fulton's book has four chapters: on historical background, on functional anatomy, on behavioral studies in animals, and on lobotomy in man. All are beautifully written, well documented, and clearly illustrated. New work in the Yale laboratories is elucidating many old and confused ideas. The last chapter, "Lobotomy in Man," is less convincing that the other three because the data are less well controlled. In fact, one wonders how well observed some of the cases have been and is skeptical about some of the optimism expressed by the clinicians.

Fulton summarizes by saying:

> In conclusion it may be said that surgical intervention for the relief of otherwise hopeless psychoses has proved a most efficacious therapeutic tool. Unfortunately, in the early stages of the development of the operation, it was used empirically, without regard for the basic physiology of this part of the brain. Within the past three years there have been two notable developments: (i) the use of a more restricted operation, and (ii) adaptation of the operation to the nature of the mental illness. In the light of the information which we now possess, I believe that the radical lobotomy as carried out by Freeman and Watts and by Lyerly should

11. Fulton, J. F.: Frontal Lobotomy and Affective Behavior: A Neurophysiological Analysis, New York, W. W. Norton & Company, Inc., 1951.

be abandoned in favor of a more restricted lesion, and that section of the medial ventral quadrant by electrocoagulation as recommended by Grantham appears to have advantages that make it superior to any other approach. This technique can no doubt be made applicable to the cingulate and will probably replace surgical resection of this part of the mesopallium. . . .

Moreover, the fibers which pass through the medial ventral quadrant appear to be those primarily concerned with the relief of intractable pain, and since their interruption can readily be achieved by electrocoagulation and since damage to tissues is minimal with this procedure and there is no trace of intellectual deficit following it, this would seem to be the operation of choice for dealing with pain.

It is perhaps too early to say that "surgical intervention for the relief of otherwise hopeless psychoses has proved a most efficacious therapeutic tool." One might better say that certainly much suffering has been relieved. One must admit that there are many failures. The electrocoagulation technique, though promising, is still far from perfect; even the size of the induced lesion is not predictable. The use of the more restricted operation is to be applauded, and toward that goal a great deal of thought and surgical skill are being directed. Because so many new facts are being found about the anatomy and physiology of these areas that determine man's psychological reactions, one is tempted to advise patients who are thinking of an elective operation to be satisfied with their present state, if it is at all tenable, and await the developments of the next year or two. By that time much progress can be hoped for in approaching Fulton's second goal, the adaptation of the operation to the nature of the mental illness.

The extensive leucotomies done so frequently at present all too often leave the patient with a most distressing mental deficit. This is especially obvious in the cases in which the operation was performed for intractable pain and in which the patient was mentally fairly normal before operation.[12] Unilateral leucotomy causes less severe and less lasting mental deficit, but for a period of months it may relieve pain to a marked degree.[13] The patients report that they still feel pain but that it does not bother them. They get along with much reduced doses of analgesic and narcotic medicaments. Fulton (page 49) believes that what has happened is that an important ascending sensory system, chiefly visceral in origin, has been removed from the sphere of consciousness. He believes (page 126) that the medial ventral quadrant of the frontal white matter carries these pain fibers from the thalamus to the cortex. One would suspect that the problem is not as simple as that. Such phenomena as the phantom limb and "pain habit" must be explained, as well as the successes and failures of the various operations that have been tried to relieve them. Why is pain in a phantom limb often but not always cured by chordotomy? What neurophysiological mechanism can explain the common statement of patients with intractable pain that after operation they "still feel the pain but it does not bother" them? Great strides have been made in this field, but there is still much to be done.

Not only do neurosurgeons relieve pain by changing the functional integration of the nervous system, but they can relieve distressing motor symptoms, such as tremor, athetosis, and spasticity. In a monograph published in Copenhagen,

12. Bonner, F. J.; Cobb, S.; Sweet, W., and White, J. C.: Frontal Lobe Surgery: Its Value in the Treatment of Pain with Consideration of Postoperative Psychological Changes, A. Research Nerv. & Ment. Dis., Proc., to be published.

13. Scarff, J. E.: Unilateral Prefrontal Lobotomy for the Relief of Intractable Pain, J. Neurosurg. **7**:330, 1950.

Meyers [14] has summarized the surgical experiments in the therapy of certain "extrapyramidal" diseases and described his own experiences. For 10 years he has been trying various operations to relieve the tremor and rigidity of Parkinson's disease. Of 38 patients subjected to various operations, 25 were improved, 7 were unimproved, and 6 died. This is a mortality of 16%. A consideration of the different surgical maneuvers used shows that the best results came from sectioning the pallidofugal fibers as they leave the striatum in the ansa lenticularis. This operation was performed on 15 patients, 10 of whom were improved, but 3 died. The other reasonably successful operation was extirpation of the head of the caudate nucleus with section of the motor fibers in the anterior part of the internal capsule. This was done in eight patients with improvement in five and one death. In six the operations were combined, with improvement in four and one death. Autopsies showed that death was usually caused by hemorrhage and softening in the brain near the site of operation. Meyers believes that the operative risks of these procedures are too great to warrant their general employment. The observations are important, and the physiological effects of these tract sections point the way, but better methods of approach must be discovered.

Better results have been obtained in a rare disease, hemiballismus. The causative lesion is usually near the subthalamic nuclei; the main symptom is a coarse, somewhat rhythmic flapping motion of the arm and sometimes the leg. It continues until death supervenes from exhaustion. Meyers has stopped this involuntary movement in two cases by making a cortical incision anterior to Area 4, separating it from Areas 4s and 6. Many operations have been tried for choreoathetosis, but the results have been variable and unsatisfactory.

CEREBRAL PALSY

"Cerebral palsy" has been recently brought to the attention of the public by a number of organizations interested in improving the treatment of children suffering from this disorder. It is an important problem because the number of patients involved is large (estimated as about 50,000 children in the United States and 10,000 in Britain). As a cause of crippling children it is second only to poliomyelitis. Nevertheless propaganda has exaggerated the extent of the problem and has raised false hope in many parents. Cerebral damage from automobile accidents is probably a much more frequent cause of disability, yet surprisingly little is done about the epidemic of highway injuries!

An excellent summary of the situation has been made by Denhoff, Smirnhoff, and Holden,[15] who accept the usual definitions, that cerebral palsy is a condition characterized by paralysis, weakness, or incoordination or any other aberration of motor function, due to malfunction of the motor centers of the brain. They add, however, that emotional and sensory factors must be considered. They make three headings under etiology: prenatal, paranatal, and postnatal. Under the first, heredity is probably the most important; Rh incompatibility with erythroblastosis fetalis and cerebral defects resulting from kernicterus is common; toxoplasmosis

14. Meyers, R.: Surgical Experiments in the Therapy of Certain "Extrapyramidal" Diseases: A Current Evaluation, Acta psychiat. et neurol., Supp. 67, 1951, pp. 1-42.

15. Denhoff, E.; Smirnhoff, V. N., and Holden, R. H.: Cerebral Palsy, New England J. Med. **245**:728 and 771, 1951.

is rare. Virus infection of the mothers during the third month can cause fetal encephalitis, but whether cerebral palsy is a common result is not known. Nutritional deficiencies of pregnant animals have been experimentally shown to cause cerebral malformations in the fetus, but the clinical significance of those experiments is still to be demonstrated.[16] Paranatal lesions are largely due to asphyxia of the infant. "Birth hemorrhage" is much talked of but rarely seen. The low oxygen tension that causes the damage may be due to excessive anesthesia and oversedation added to the mechanical risks of delivery. Prematurity adds greatly to the risk of asphyxia. Postnatally the cerebral damage may be caused by encephalitis of various sorts, especially measles encephalitis. The list here includes all the cerebral diseases of childhood and is limited only by a definition of how late in development one believes "cerebral palsy" may appear. The British choose the age of 18.[17] Accurately speaking, of course, a hemiplegia at 65 is just as much a "cerebral palsy" as a paranatal asphyxia with paralysis. But the term is now generally used to mean the cases occurring in early childhood in which, added to the cerebral injury, there is the problem of an injury occurring during the growth and development of the brain. Physiologically and psychologically the clinical results are different from the results of lesions in an adult brain.

Benda [17] points out in his thorough discussion that although 7 children with cerebral palsy are born each year in each population of 100,000, 1 of these dies in infancy and 2 are definitely feebleminded, so that they cannot be treated constructively. The four remaining will have relatively normal mental capacities and make up the case load for treatment. Of these the symptoms of one will probably be so mild as to need little if any treatment; two will be capable of great improvement, and one will have so much motor difficulty as to be relatively hopeless. It is important to bring out these sobering statistics to contravert the too optimistic "publicity" of those who are trying to raise money for the "rehabilitation of spastics."

In discussing etiology, Benda emphasizes the importance of asphyxia as the principal cause of birth injury. Although hemorrhage is found in 25% of children that are born dead, "birth hemorrhage" is not a common cause of cerebral palsy because it is so often fatal. As Wyllie [18] expresses it: "To base suppositions of morbid anatomy in the survivors upon post-mortem material is unwise." His excellent paper lays more stress on the prenatal factors in etiology, especially inheritance; many of the spastic diplegias that used to be classified as "Little's disease" are due to hereditary cerebral defects.

All the authors cited discuss treatment. It is important to recognize the spastic child early and to begin physical therapy within the first year if possible. The athetoid children are usually not recognized at so early an age, and, since their training depends more upon relaxation, the child must be older to cooperate in treatment. Benda emphasizes the emotional needs of these children. It is obvious that the treatment can be carried on only at centers where trained experts can work with the aid of special apparatus. The emotional trauma to the child caused by

16. Ingalls, T. H.: Biologic Implications of Mongolism, in Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952.

17. Benda, C. E.: Developmental Disorders of Mentation and Cerebral Palsies, New York, Grune & Stratton, Inc., 1952.

18. Wyllie, W. G., in Modern Trends in Neurology,[7] Chap. IV.

separation from the family must be understood and taken into consideration. Spitz [19] has discussed the effect of disrupted relationships between mother and child and shown that anaclitic depressions and marasmus may result.

HORMONES AND MENTAL SYMPTOMS

The relation of emotional disorders to the autonomic nervous system and the endocrine glands was briefly reviewed in 1950.[20] It was already known at that time that patients treated with cortisone and corticotropin (ACTH) sometimes showed pathological changes of mood and behavior. The earlier reports were of a case or two, warning against the too-free use of these hormones.[21] Clark and associates [22] collected 18 cases of mental change among a series of 56 treated patients. The changes in only six of them were severe enough to warrant the diagnosis of psychosis, but that number represents a high percentage. The psychotic episodes were usually brief, lasting only a few days, but some have lasted for months. They have shown a varied symptomatology, including all the common phenomena of affective and schizoid psychoses. The commonest picture is a "slap-happy" euphoria; this may be all there is to the mental reaction, and it may pass off in three or four days. On the other hand, it may persist, lead to manic behavior, and end with a period of depression. The severer reactions include delusions, hallucinations, and catatonia. The psychiatric symptoms are variable and change from day to day. The occurrence of these mental symptoms does not seem to bear any relation to a history of previous mental disorder. No correlation has yet been found with the amount of hormone given or with physiological chemistry. Some authors believed [23] that the symptoms were related to a loss of potassium, but this has not been proved. Active work is under way in many centers to discover the cause of the mental aberrations.

From the standpoint of the psychiatrist, this is a most significant lead to future research into the cause of schizophrenia and manic-depressive psychosis. Here are two hormones that have repeatedly precipitated short schizophrenic, manic, or depressive reactions in persons who had previously shown no tendency to psychiatric disorder. The fact that manic-depressive symptoms are mixed with the schizophrenic symptoms in these patients emphasizes the point of view held by some psychiatrists [24] that schizoid and affective psychoses are variants of one general

19. Spitz, R. A., in The Psychoanalytic Study of the Child, edited by R. S. Eissler and others, New York, International Universities Press, Inc., 1951, Vol. 6, p. 255.

20. Cobb, S.: Review of Neuropsychiatry for 1949, Arch. Int. Med. **85**:998, 1950.

21. Dutoit, C. H., and Bauer, W.: Effect of ACTH on Ulcerative Colitis, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950. Galdston, M.; Weisenfeld, S.; Benjamin, B., and Rosenbluth, M. B.: Effects of ACTH in Chronic Lung Disease, Am. J. Med. **10**:166, 1951. Irons, E. N.; Ayer, J. P.; Brown, R. G., and Armstrong, S. H.: ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses, J. A. M. A. **145**:861, 1951.

22. Clark, L. D.; Bauer, W., and Cobb, S.: Preliminary Observations on Mental Disturbances Occurring in Patients Under Therapy with Cortisone and ACTH, New England J. Med. **246**:205, 1952.

23. Ranshoff, W.; Brust, A., and Mirsky, I. A.: The Effects of Sodium and Potassium on the Metabolic and Physiologic Responses to ACTH, Proc. Central Soc. Clin. Research **23**:86, 1950; Proceedings of Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951.

24. Cobb, S.: Foundations of Neuropsychiatry, Ed. 2, Baltimore, Williams & Wilkins Company, 1941.

disease. Although in typical cases these two types of psychosis are quite different and easily separated nosologically, they are the extremes of a continuous series of variables. In other words, if cases with purely manic-depressive symptoms are put at one end of the series and cases with purely schizophrenic symptoms at the other, the space between can be filled in with a long series of cases which are mixtures: near one end will be examples of depression or mania with "schizophrenic coloring," near the other, schizophrenia with depressive elements or cyclic mood swings. There are a few cases described in which the symptoms are entirely schizophrenic but run in cycles. In the midzone of this series are cases that cannot be diagnosed as either schizophrenia or cyclothymia and so are called schizoaffective psychosis.

There has for a long time been evidence that endocrine disorder caused mental changes. Every physician is familiar with the mental symptoms of hyperthyroidism and hypothyroidism. Chronic insufficiency of the adrenal glands (Addison's disease) often causes restlessness, apprehension, and extreme irritability. Panhypopituitarism is sometimes accompanied with depression and paranoid delusions. A patient recently presented at the clinicopathological conference at the Massachusetts General Hospital [25] had an extraordinary history of neuropsychiatric symptoms. He first came to the clinic for "muscle stiffness" 11 years ago and the diagnosis of myotonia was made, probably part of the syndrome of "myotonia dystrophica." He was relieved of the myotonic symptom by taking quinine and returned to his occupation of professional golfer. A note was made at the time that he should be observed for signs of pituitary tumor, because the roentgenograms of the sella turcica showed some erosion and because the muscular disease was probably endocrine in origin. For several years he was well and then began gradually to become asthenic. He returned to the hospital with a full-blown syndrome of panhypopituitarism, with bitemporal hemianopsia and a roentgenogram indicating a large tumor of the pituitary. He was given corticotropin and on the third day went into a depressive and delusional psychosis that made operation on the tumor impossible. He died 10 days later, and autopsy showed a large hypophysial adenoma pressing upward upon the hypothalamus.

Cushing's syndrome, whether caused by basophilic adenoma of the pituitary or by adrenocortical hyperplasia, is often accompanied with severe mental symptoms [26] that may sometimes be quickly relieved by operative removal of the adrenal tumor. Some cases have shown lesions of the brain and changes in the spinal fluid. The mental disturbances of late pregnancy and the puerperium may be closely related to hormonal readjustments.

Recently, Hill, Loe, Theobald, and Waddell [27] have submitted schizophrenic patients to a stress situation, namely, insulin hypoglycemia. Their reactions were measured by electroencephalograph, skin resistance records, and electrocardiograph for heart rate. From controls it was determined that the normal homeostatic mechanism in hypoglycemia is a change in electroencephalographic rhythm from

25. Cases from the Medical Grand Rounds, Massachusetts General Hospital, Am. Pract. & Digest Treat., to be published.

26. Spillane, J. D.: Nervous and Mental Disorders in Cushing's Syndrome, Brain **74**:72, 1951. Trethowan, W. H., and Cobb, S.: Neuropsychiatric Aspects of Cushing's Syndrome, A. M. A. Arch. Neurol. & Psychiat. **67**:283, 1952.

27. Hill, D.; Loe, P.; Theobald, J., and Waddell, M.: A Central Homeostatic Mechanism in Schizophrenia, J. Ment. Sc. **97**:111, 1951.

"alpha" to "theta," followed by discharge of the sympathetic adrenal system, as shown by a sudden fall in electrical skin resistance and by a rise in heart rate. In schizophrenic patients the level of blood sugar at which the "theta" rhythm appears in the brain is significantly lower, and the time at which this activity appears is significantly later. These observations indicate a cerebral control of the response to this stress and suggest a disorder of this central homeostatic mechanism in schizophrenia.

Other hormones might be mentioned that seem to bear a relation to mental disease, by either their lack or their excess. Many have been given as therapeutic agents. The most extensively used in treatment is insulin for schizophrenia. The early enthusiasm for this therapy has not been justified by statistical study of results. Mayer-Gross and Royal [28] conclude that if insulin is given within the first year of illness only 55 to 60% of patients respond favorably. After two years of schizophrenic illness, the results from insulin treatment seem to be no better than those from simple supportive institutional care. Even the good results in the first year are minimized by the fact that in many early cases there are spontaneous remissions and even permanent recovery.

Corticotropin, cortisone, thyroid, gonadal, and other hormones have been tried as therapeutic agents in many forms of mental disturbances. The results have been conflicting and the successes few. It seems to be easier to cause than to cure psychosis by manipulating hormones. Discouragement, however, should not prevail because of these observations. Data are rapidly accumulating that show an undoubted relation between endocrine glands and brain. These data are so significant and illuminate the problem from so many angles that it seems reasonable to hope that much will be learned soon about the etiology of schizophrenia, the greatest contemporary problem in psychiatry, and one of the greatest in all medicine.

28. Mayer-Gross, W., and Royal, C.: Insulin Coma Therapy of Schizophrenia: Some Critical Remarks on Dr. Sakel's Report, J. Ment. Sc. **97**:132, 1951.

News and Comment

ANNOUNCEMENTS

Seventeenth Annual Convention of the National Gastroenterological Association.—The National Gastroenterological Association will hold its Seventeenth Annual Convention and Scientific Sessions at the Hotel Statler in New York City on Oct. 20, 21, and 22, 1952. Included in the program will be a Symposium on Liver Diseases, a Symposium for the General Practitioner, a Symposium on Bleeding Esophageal Varices and the Problems of Portal Hypertension, and a panel discussion on "Gastrointestinal X-Ray Methods, Diagnosis and Treatment." Immediately after the convention, on Oct. 23, 24, and 25, 1952, the Association will conduct its Fourth Annual Course in Postgraduate Gastroenterology at the Hotel Statler in New York City. Further information concerning the program and details of the Postgraduate Course may be obtained by writing to the Secretary, National Gastroenterological Association, 1819 Broadway, New York, 23.

Books

Food and Nutrition. Second edition. By E. W. H. Cruickshank, M.D. Price, $6.50. Pp. 454, with 51 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

This is a book on food and nutrition which is different. It does not deal with the intimate biochemistry and physiology of the essential nutrients or with an extensive description of clinical deficiency states as found in the usual text on nutrition in this country. Rather, the general subject of practical human nutrition, not the nutrition of the individual but the nourishment of a nation, is discussed in a comprehensive and statesman-like fashion. In essence, Dr. Cruickshank has attempted to set forth the basic facts which govern the nutritional well-being of a population. The practical application of these facts is illustrated by a detailed and documented account of the way in which the United Kingdom handled its difficult food problems during and after World War II.

Sufficient knowledge now exists to allow intelligent management of a nation's food supply so that malnutrition can be prevented. In Great Britain, during and after the last war, this knowledge was consciously applied in the management of a nation's food resources, so that the nutritional health of the nation actually improved rather than deteriorated. This fact is all the more noteworthy since the supply of food was somewhat limited quantitatively and especially restricted in the supply of protective foods.

The book has a strong historical flavor throughout. In it the facts on nutrition in Great Britain from 1939 to 1950 are collected. While one may not always agree with the historian's interpretations of the facts, the mere collection and organization of these data, much of it otherwise difficult to obtain, represents a very valuable contribution. Throughout the book, it is evident that the author writes with an authority and a familiarity which can come only from long and intimate association with the subject discussed. From the vantage point of 1951, Dr. Cruickshank looks back with perspective and extracts the valuable essence of past history with a view to applying it in the future.

This book will be of interest to all in the field of nutrition. It will be invaluable to those concerned with the food policies and programs of a nation, not only in normal times but especially in national or international emergencies which necessitate more rigorous application

of scientific principles in the control of food production, processing, and distribution. The chapters on the bread controversy, i. e., high-extraction wheat-flour bread versus enriched white-flour bread, on the assessment of nutritional status, on dietary standards and diet planning, and on food technology are especially interesting. Those well versed in the technical aspects of nutritional biochemistry and physiology will note some minor inaccuracies of scientific fact, but these do not distort the important practical lessons which the book does convey.

Elementary Medical Statistics. By Donald Mainland, M.B., Ch.B., D.Sc., F.R.S.E., F.R.S.C. Price, $5. Pp. 327, with 23 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

The author states that this book is designed primarily for students who are to become practitioners. The physician who is seriously interested in becoming acquainted with the principles of statistical analysis as applied to medicine will appreciate the style of writing and the manner in which the author has presented the subject. In particular, the reader can obtain an appreciation of the problems in research, sampling, errors, tests of significance, and so forth, without having to wade through masses of formulae and numerical computation. The material has been organized under eight chapter headings; under each chapter heading within the table of contents is given an outline of the material presented in the chapter. An introduction is given to each chapter with a bit of advice to the reader on the contents and their value. In one instance the author says: "Mostly, however, it is a chapter to read and think about." This statement could well be applied to the book as a whole. Numerous practical examples are presented throughout the text, some illustrating poor methods of research. At the end of several chapters a series of questions is asked the reader in order to test his comprehension of the principles described. The answers to these questions are found in the back of the book. This book should be well received. The author is to be commended both on the quality of the statistical contents and on his novel method of preparing the book.

The 1951 Year Book of Endocrinology (January, 1951-January, 1952). Edited by Gilbert S. Gordon, M.D., Ph.D. Price, $5. Pp. 415, with 102 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This book is a continuation of a series started many years ago. Many selected papers are abstracted by the editor and grouped under certain major headings.

In general, the abstracts are clearly given and are illustrated from time to time by charts and photographs. Editorial comments in some cases are pertinent, in other cases immaterial, and in some cases erroneous. The book is very useful for the busy general physician who would like to get a quick view of a year's work in endocrinology. Those interested primarily in this field naturally would wish to read the papers themselves *in extenso*.

Vascular Diseases in Clinical Practice. Second edition. By Irving Sherwood Wright, M.D. Price, $8.50. Pp. 552, with 116 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This edition, the second, of Dr. Wright's excellent book on vascular diseases adds some new material but follows closely the plan of the first issue. This treatise deals in systematic and comprehensive fashion with every conceivable disorder of arteries, veins, and lymphatics; the enumeration of diagnostic and therapeutic procedures is indeed complete.

However, the discussions are precise, not too complicated for the practitioner, and documented with excellent bibliographies. The illustrations and diagrams are extremely helpful. Throughout one feels the authoritative touch which comes only when a writer has actually done firsthand work in the field.

The reviewer, perhaps too sensitive to accurate English usage, was a bit shocked to read in the preface that man is almost constantly "hemorrhaging and thrombosing." Needless to say, no such verbs are to be found in the Oxford or in Dorland's dictionaries; however, in a day when the roentgenologists speak of "positioning" a patient and those who stand are called "standees," one probably should not be too fussy.

Bacitracin. By Members of the Research Division, S. B. Penick & Company. Price not given. Pp. 127, with 31 tables. S. B. Penick & Co., 50 Church Street, New York, 1952.

This book is nothing more than an annotated bibliography on bacitracin. It contains a few statements that embrace generalities concerning antibiotic agents which are good. It is obviously a conspicuous effort to make bacitracin look better than it actually is from the standpoint of antibiotic therapy. The volume does not emphasize the nephrotoxic properties of bacitracin which seriously limit the use of this antibiotic in clinical medicine. On the contrary, the nephrotoxicity of this agent is deprecated, and efforts are made in certain portions of the book to explain nephrotoxicity on a basis other than that of the drug itself. Contrary to what is said in this work, bacitracin is hardly the drug of choice in the treatment of amebiasis. It certainly is of little or no value, despite the authors' contentions, in the treatment of ulcerative colitis and in the preoperative preparation of patients for operations on the bowel. Affirmative claims in respect to these factors are only a few of the many statements in this book which are hardly warranted on the basis of present-day knowledge.

The book is said to be written for the purpose of discussing the status of bacitracin in the armamentarium of the general practitioner, as well as the specialist. The book contains little that would be of value to either. It is a pretentious brochure.

Observations on the General Effects of Injury in Man, with Special Reference to Wound Shock. By R. T. Grant and E. B. Reeve. Medical Research Council Special Report Series No. 277. Price, 8s. 6d. Pp. 313, with 19 illustrations. His Majesty's Stationery Office, Box 569, London, S. E. 1, 1951.

This monograph deals with injuries, with special reference to wound shock. The volume is compiled along the usual lines of these publications and contains much valuable material, including specific case reports. Most of this information, however, which was gleaned during the war, is more or less common knowledge at present. Such matters are discussed as blood pressure related to blood loss, response to transfusion, course during and after operation, and special features of various types of injury. However, it is very useful to have the British experience condensed between two covers, and anyone working in this field will wish to have it.

Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions. By Myron Prinzmetal, M.D.; Rexford Kennamer, M.D.; Eliot Corday, M.D.; John A. Osborne, M.D.; Joshua Fields, M.D., and L. Allen Smith, M.D. Modern Medical Monographs. Price, $4. Pp. 110, with illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

This book presents the authors' concept of the mechanism for the Wolff-Parkinson-White syndrome. That the syndrome may not always be due to an aberrant bundle is not a new idea. Of course, it may still be produced by such a bundle when the latter is present. This syndrome has received much attention, probably considerably more than it deserves. This monograph describes the experience of the authors with their researches and presents their impressions of the mechanism for the Wolff-Parkinson-White syndrome. The monograph should interest those who are concerned about the syndrome.

Angiocardiography. By Charles T. Dotter, M.D., and Israel Steinberg, M.D. Annals of *Roentgenology*, Series of Monographic Atlases, Volume XX. Price, $16. Pp. 304 with 635 illustrations. Paul B. Hoeber, Inc. (Medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1951.

This is an excellent discussion of angiocardiography written by one of the originators of the technique. The material is clearly presented and the monograph contains a detailed discussion of apparatus, methods, preparation of the patient, and advice regarding precautions. There are many valuable and clear illustrations concerning technique. The roentgenographic equipment is also well discussed. The method is followed by chapters on the normal angiocardiogram and its pattern in abnormal states, including disease of the aorta, various types of heart disease, including congenital defects, disease of the mediastinum, and pulmonary disease. The book will prove of value for reference and is recommended without reservation to all interested in present-day angiocardiography. It should be read by everyone concerned with applications of this method to both clinical and research medicine.

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1. Humphreys, P., et al: Angiology 3:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med., 52:2012-2014 (Aug. 15) 1952. 3. Perlman, A.: Angiology 3:16 (Feb.) 1952. 4. Samuels, S.S., et al.: Angiology 3:30 (Feb.) 1952.

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2. Heller, E. M.: The Treatment of Essential Hypertension. *Canad. Med. Assn. Jour.*, 61:293-299, Sept., 1949.

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